Guidance for Industry

Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations

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HIGHLIGHTS OF THE 1999 GUIDANCE

This document addresses FDA's recommendations for chemistry information that should be submitted in a premarket notification (PMN) for a food-contact substance (FCS). These recommendations are based on an adaptation and revision of the June, 1995 document for indirect food additive petitions entitled "Recommendations for Chemistry Data for Indirect Food Additive Petitions." Highlights of this document include:

- Alternate approaches to estimating migration to food, such as migration modeling, are presented.
- Consumption factors (CFs) for several specific polymer packaging categories, such as polyolefins, cellophane, and nylons, have been updated.
- Testing for "wet-end" additives used in the manufacture of paper and paperboard is discussed.
- FDA Form No. 3480 "Notification for New Use of a Food Contact Substance" is attached.

TABLE OF CONTENTS

I. **INTRODUCTION** 5

II. **CHEMISTRY INFORMATION FOR PREMARKET NOTIFICATIONS** 6
- A. IDENTITY 6
- B. USE 7
- C. INTENDED TECHNICAL EFFECT 8
- D. MIGRATION TESTING & ANALYTICAL METHODS 8
  - 1. Design of the Migration Experiment 9
    - a. *MIGRATION CELL* 9
    - b. *TEST SAMPLE* 10
    - c. *FOOD SIMULANTS* 11
    - d. *TEMPERATURE AND TIME OF TEST* 12
    - e. *END TESTS* 13
  - 2. Characterization of Test Solutions & Data Reporting 13
  - 3. Analytical Methods 14
    - a. *DESCRIPTION OF THE METHOD* 14
    - b. *STANDARD CURVES* 14
    - c. *EXAMPLES OF SPECTRA OR CHROMATOGRAMS* 15
    - d. *EXAMPLE CALCULATIONS* 15
    - e. *VALIDATION OF ANALYTICAL METHODS* 15
  - 4. Migration Database 16
  - 5. Migration Modeling 17
- E. CONSUMER EXPOSURE 17
  - 1. Calculation of Exposure 18
    - a. *CONSUMPTION FACTOR* 18
    - b. *FOOD-TYPE DISTRIBUTION FACTOR* 18
    - c. *CONCENTRATION IN THE DAILY DIET AND EDI* 18
    - d. *CUMULATIVE EXPOSURE* 19
  - 2. Exposure Refinement 19

APPENDIX I

FATTY-FOOD SIMULANTS FOR SPECIFIC POLYMERS 21

APPENDIX II

SELECTED MIGRATION TESTING PROTOCOLS 22
1. General Protocols (Single-Use Applications) Corresponding to Condition of Use 22
2. Adjuvants for Polyolefins 24
3. Adjuvants for Polymers (other than Polyolefins)
   Adjuvants for More than One Polymer 24
4. Articles Intended for Repeated Use 24
5. Coatings for Cans 25
6. Uncoated & Clay-Coated Papers with Latex Binders 25
7. Specially Treated Papers 25

8. Adhesives (Room temperature or below) 25
9. Laminates & Coextrusions 26
10. Boil-In-Bags 26
11. Special High-Temperature Applications 26
  a. *DUAL-OVENABLE TRAYS* 26
  b. *MICROWAVEABLE CONTAINERS* 26
  c. *MICROWAVE HEAT-SUSCEPTOR PACKAGING* 27
12. Colorants for Plastics 27
13. Dry Foods with Surface Containing No Free Fat or Oil 27
14. Wet-End Additives used in the Manufacture of Paper and Paperboard 28

APPENDIX III

ILLUSTRATIVE EXAMPLE OF VALIDATION OF ANALYSES 29

APPENDIX IV

CONSUMPTION FACTORS, FOOD-TYPE DISTRIBUTION FACTORS, AND EXAMPLE OF EXPOSURE ESTIMATE CALCULATIONS 30

APPENDIX V

REFERENCES 35

I. INTRODUCTION

Section 309 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) amends Section 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 348) to establish a premarket notification (PMN) procedure as the primary method by which the Food and Drug Administration (FDA) regulates food additives that are food contact substances (FCS). A food contact substance is any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if the use is not intended to have any technical effect in the food.

Notifications for food contact substances must contain sufficient scientific information to demonstrate that the substance that is the subject of the notification is safe for the intended use (21 U.S.C 348(h)(1)). Because the safety standard is the same for all food additives, whether subject to the petition process or the PMN process, information in a PMN should be comparable to that recommended for inclusion in a food additive petition.

This guidance has been prepared by the Office of Premarket Approval of the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration in accordance with FDA's "Good Guidance Practices" (62 FR 8961; Feb. 27, 1997). The purpose of this document is to provide general guidance for the chemistry information that should be included in a PMN for an FCS. The guidance represents FDA's current thinking on the chemistry information for a PMN. It does not create or confer any rights for or on any person and does not operate to bind the Agency or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute and regulations. For situations not addressed in this guidance, notifiers are advised to consult FDA. Periodically, FDA will update this guidance in light of new information.

II. CHEMISTRY INFORMATION FOR PREMARKET NOTIFICATIONS

The chemistry information that FDA recommends to support the proposed use of an FCS is described in Section III, items C through F, of the guidance document, entitled "Preparation of Premarket Notifications for Food Contact Substances: Administrative." This information is reproduced below in italics, followed by a detailed discussion of each recommendation. A clear and concise presentation of the information in the format described below will facilitate review of the PMN.

A. IDENTITY

Item C: Notifications should include detailed information on the chemical identity of the FCS and of the impurities and residual reactants from the production of the FCS including, where possible, the chemical and structural formula and the Chemical Abstract Service (CAS) Registry Number.

Identity information is used to describe the FCS that is the subject of a PMN and to identify substances that may migrate into food from use of the FCS. Migrating substances may include not only the FCS itself, but also degradation products and impurities in the FCS that may have no functional effect.

Information identifying the FCS should be as complete as possible with respect to its name, composition, and method of manufacture. These items include:

1. Chemical Name. The IUPAC or Chemical Abstracts name is acceptable.

2. Common or Trade Names. These should not be the only means of identification. FDA does not maintain a compilation of common or trade names.

3. Chemical Abstracts Service Registry Number[1].

4. Composition. A full description of the composition of the FCS is used to compile a list of potential migrants to food. This should include chemical formulae, structures, molecular or formula weights for single compounds or components of commercial mixtures. For polymers, notifiers should also submit the weight average ($\bar{M}_w$) and number average ($\bar{M}_n$) molecular weight, molecular weight distribution information, and the methods used for their determination. If the molecular weight is not readily obtainable, the notifier should furnish other properties of the polymer that are functions of the molecular weight, such as intrinsic or relative viscosity or melt flow index.

In addition, the notifier should provide the following information:

a. A complete description of the manufacturing process, including purification procedures, and the chemical equations for all steps of the synthesis.

b. A list of reagents, solvents, catalysts, purification aids, etc., used in the manufacturing process, the amounts or concentrations used, their specifications, and their CAS Reg. Nos.

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[1] CAS Registry Numbers for new compounds and assistance with nomenclature can be obtained by writing to Chemical Abstracts Service (CAS) Client Services, 2540 Olentangy River Road, P.O. Box 3343, Columbus, OH 43210, or by visiting their website at http://www/cas/org/support/client.html.

c. Chemical equations for known or likely side reactions occurring during manufacture of the FCS, including catalyst degradation reactions, if known.

d. Concentrations of all major impurities (e.g., residual starting materials, including all reactants, solvents, and catalysts, in addition to byproducts and degradation products) together with supporting analytical data and calculations. In the case of polymers, concentrations of residual monomers should be included.

e. Spectroscopic data to characterize the FCS. In some cases an infrared (IR) spectrum is sufficient, but occasionally other information, such as visible and ultraviolet absorption spectra or nuclear magnetic resonance (NMR) spectra, are more useful.

Those data and information not intended for public disclosure, such as trade secret or confidential commercial information, should be so identified.

5. Properties. Notifiers should submit the physical and chemical specifications of the FCS (e.g., melting point, impurity specifications). Notifiers should report properties that can affect migration potential, such as solubilities in food simulants. In the case of new polymers, notifiers should provide glass transition temperatures, ranges for densities and melt flow indices, and information on morphology (e.g., degree of crystallinity) and stereochemistry. For new adjuvants in regulated polymers, notifiers should submit information on the properties of the polymer (e.g., T_g) used in migration testing.

6. Analyses. If the FCS is a component of an otherwise regulated material (e.g., an antioxidant in a regulated polymer), notifiers should provide analytical methods for determining the FCS in the material. Notifiers should submit supporting analytical data (refer to Section II.D.3).

B. USE

Item D: Notifications should include detailed information on the intended conditions of use of the food contact material manufactured with the food contact substance (e.g., maximum use temperature, type of food with which the substance is intended to come into contact, duration of the contact, and whether the food contact material is intended for repeat or single use application.)

Notifiers should examine general use limitations in notifications and regulations for similar food contact substances and propose a comprehensive set of limitations on the notified use. Certain of these limitations may be the basis for assumptions made in deriving exposure estimates for the FCS. Any applicable limitations should be included in the description of the notified use. In the absence of appropriate limitations, FDA may be required to use assumptions in estimating exposure that would result in more conservative values for certain classes of FCS.

1. Notifiers should provide the maximum use level of the FCS and the types of food-contact articles in which it may be used. "Use level" refers to the concentration of a substance in the food-contact article, not in the food. Notifiers should state the range of possible uses, such as films, molded articles, coatings, etc., and report the anticipated maximum thickness and/or weight per unit area of these articles.

2. Notifiers should list the types of food (with examples) expected to be used in contact with the FCS and the maximum temperature and time conditions of food contact[2]. Classifications that may be helpful are given in 21 CFR 176.170(c), Table 1 (Types of Raw and Processed Foods) and Table 2, which lists various conditions of use. These tables are not all-inclusive, however.

C. INTENDED TECHNICAL EFFECT

Item E: Notifications should include a statement of the intended technical effect of the food contact substance, and data that demonstrate the minimum amount of the substance that will achieve the intended technical effect.

Notifiers should present data to show that the FCS will achieve the intended technical effect and that the proposed use level is the minimum level required to accomplish the intended technical effect. In these circumstances, "technical effect" refers to the effect on the food-contact article, not on the food. An example would be the effect of an antioxidant in preventing oxidative degradation of a particular polymer. In the case of a new polymer, notifiers should present data that demonstrate the specific properties of the polymer that make it useful for food-contact applications. This information is frequently available in product technical bulletins.

In cases where the use level of an FCS is self-limiting, notifiers should provide supporting data.

D. MIGRATION TESTING & ANALYTICAL METHODS

Item G: Notifications should include sufficient data to enable FDA to calculate the estimated daily intake (EDI) resulting from the intended use of the substance, including levels of residual reactants and impurities.

A notifier should provide information sufficient to permit estimation of the EDI of the FCS, i.e., consumer exposure. FDA will calculate the concentration of the FCS expected in the daily diet from analyzed or estimated levels of an FCS in food or food simulants. A more complete discussion of this topic is given in Section II. E. and Appendix IV.

The concentration of an FCS in the daily diet may be determined from measured levels in food or in food simulants, or estimated using information on formulation or residual levels of the substance in the food contact article and the assumption of 100% migration of the FCS to food. Although FDA has always accepted reliable analyses of FCS in real foods, in practice, many analytes are difficult to measure in food. As an alternative, notifiers may submit migration data obtained with food simulants that can reproduce the nature and amount of migration of the FCS into food. Because an FCS may be used in contact with many foods with different processing conditions and shelf lives, the submitted migration data should reflect the most severe temperature/time conditions to which the food-contact article containing the FCS will be exposed.

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[2] Migration into food depends on the chemical structure of the FCS, the nature of the food matrix contacting the FCS, the type of food with which it is in contact, and the temperature and duration of food contact. Prior to the submission of a PMN, a potential notifier may wish to meet or correspond with FDA to discuss appropriate migration testing protocols (see Section III).

Before undertaking migration studies, the notifier should carefully consider the potential uses of the FCS. If, for example, use at temperatures no higher than room temperature is anticipated, it makes little sense to conduct migration experiments that simulate high temperature food contact. Such experiments might lead to elevated levels of the FCS in the food simulants that might require a more extensive toxicological data package to support the exaggerated exposure. In some cases where the use level of the FCS is low, it may be possible to dispense with migration studies altogether by assuming 100% migration of the FCS to food. The following example illustrates this approach:

> Consider an adjuvant added prior to the sheet-forming operation in the manufacture of paper. If analysis or calculation shows that the final adjuvant concentration in paper cannot exceed 1 mg/kg and the basis weight of the finished paper is 50 pounds/3000 ft^2, or 50 mg/in^2, then the maximum weight of adjuvant per unit area of paper is 1×10^{-6} g adjuvant/g paper x 50 mg/in^2 = 0.000050 mg/in^2. If all the adjuvant migrates into food and 10 grams of food contacts 1 square inch of paper (FDA's default assumption), the maximum concentration in food would be 5 μg/kg. It may be expected that this low concentration in food would lead to commensurately low EDI of the FCS. Therefore, although migration studies could result in further lowering of the estimate of daily intake, such studies might be unnecessary.

Levels in food should be based on the results of migration testing or other methods as applicable, so as to reflect as closely as possible the actual use conditions of the food contact article containing the FCS. In general, migration values determined using the assumption of 100% migration to food should be avoided to reduce conservatisms to the greatest extent possible.

1. Design of the Migration Experiment

a. *MIGRATION CELL.* When use of an FCS is anticipated with one particular type of package, such as a beverage bottle, packages may be filled with food simulants and tested. For more general uses or when the package surface area does not produce sufficient extractives for adequate characterization, a migration cell should be used in which a specimen of known surface area is extracted by a known volume of simulant. The two-sided migration cell described by Snyder and Breder (Snyder and Breder, 1985) is recommended. Although this specific cell may not be universally applicable, FDA recommends that two of its essential features be incorporated in modified designs. These features are:

(1) Polymer plaques of known surface area and thickness (see Section II.D.1.b for further discussion) are separated by inert spacers (such as glass beads) so that simulant flows freely around each plaque. Migration from the plaque is considered to be two-sided.

(2) The headspace is minimized, and gas-tight and liquid-tight seals are maintained. (Minimum headspace and gas tightness are of lesser importance if the migrant of interest is non-volatile.)

Additionally, and importantly, the cell should be subjected to mild agitation to minimize any localized solubility limitation that might result in mass-transfer resistance in the food simulant.

For applications in which a two-sided cell design is not suitable, such as laminate constructions, the notifier may refer to the references in Appendix V for applications describing other cell designs. The notifier may also devise an alternative cell. FDA is willing to comment on any such design prior to performance of the migration experiment.

b. *TEST SAMPLE.* Some important considerations are the following:

(1) *Formulation*: Use the highest proposed concentration of the FCS in the food-contact article in preparing samples for migration testing. Notifiers should provide information that characterizes resin samples used in testing, including the concentrations and identities of other components that may be present, the chemical composition of the resin (including co-monomer content where appropriate), molecular weight range, density, and melt flow index. <u>If the formulation is plasticized</u>, the most highly plasticized formulation should be used for testing.

(2) *Sample Thickness & Surface Area*: Report both the thickness of the test plaque and surface area of the sample tested. If a plaque is tested by immersion and is of sufficient thickness to ensure that the initial FCS concentration at its center is unaltered by migration that occurs from both sides during the test period, the surface area of both sides can be used to calculate migration (units of mg/in^2).

Migration may be considered to be independent from both sides of the sample if the sample plaque <u>thickness is at least 0.05 cm (20 mil or 0.020 in) and not more than 25 percent of the FCS has migrated by the end of the experiment</u>. If these conditions are not met, the surface area of only one side should be used in the calculation and consideration should be given in the PMN to proposing a limitation on film thickness.

(3) *Polymer Properties*: If the FCS is a <u>polymer adjuvant</u>, notifiers should perform migration testing on the polymer with the lowest average molecular weight. If the FCS is a <u>new polymer</u>, notifiers should test the polymer that would be expected to give the highest levels of extractives, i.e., the polymer with the lowest average molecular weight, percent crystallinity, and degree of cross-linking.

c. *FOOD SIMULANTS*. The following food simulants are recommended. Additional discussion on this subject is found in Appendix I.

Food-Type as defined in 21 CFR 176.170(c) Table 1	Recommended Simulant
Aqueous & Acidic Foods (Food Types I, II, IVB, VIB, and VIIB).	10% ethanol[a]
Low- and High-alcoholic Foods (Food Types VIA, VIC).	10% or 50% ethanol[b]
Fatty Foods (Food Types III, IVA, V, VIIA, IX).	Food oil (e.g., corn oil), HB307, or Miglyol 812[c]

a- for exceptions, see main text.
b- actual ethanol concentration may be substituted (see main text and Appendix II).
c- HB307 is a mixture of synthetic triglycerides, primarily C_{10}, C_{12}, and C_{14}. Miglyol 812 is derived from coconut oil (see main text and Appendix I).

When food acidity is expected to lead to significantly higher levels of migration than with 10% ethanol, or if the polymer or adjuvant is acid-sensitive, or if trans-esterification occurs in ethanol solutions, separate extractions in water and 3% acetic acid in lieu of 10% ethanol should be conducted[3].

10% ethanol is intermediate in alcohol concentration between wine and beer. Migration levels to wine and beer are not expected to be very different from 10% ethanol values. Therefore, test results developed with 10% ethanol can generally be used to evaluate exposures and support clearances for contact with alcoholic beverages having up to 15 volume-% ethanol.

Unsaturated food oils (like corn and olive oils) can be difficult matrices for the analysis of a migrant because these oils are susceptible to oxidation, especially at high temperature. Miglyol 812, a fractionated coconut oil having a boiling point range of 240 to 270°C and composed of saturated C_8 (50-65%) and C_{10} (30-45%) triglycerides, is an acceptable alternative fatty-food simulant for migration testing.[4] HB 307, a mixture of synthetic triglycerides, primarily C_{10}, C_{12}, and C_{14}, is also useful as a fatty-food simulant.[5]

In some cases, analysis of a migrant in a food oil will not be practical and a simple solvent must be used. There does not appear to be one solvent that will effectively simulate a food oil for all polymers. <u>A list of various polymers and their recommended fatty-food simulants appears in Appendix I</u>. For other polymers,

[3] In the past, FDA recommended 8% ethanol as an aqueous food simulant. Increasing the ethanol concentration from 8% to 10% will have a minimal impact on migration studies conducted on adjuvant/polymer systems. This change also harmonizes more closely FDA's migration protocols with those of other nations. See the reference list at the end of Appendix II relating to FDA's development of the use of food simulants.

[4] Miglyol 812, a product of Dynamit Nobel Chemicals, is available from HULS America, Inc., 80 Centennial Ave., P. O. Box 456, Piscataway, NJ 08855-0456.

[5] HB307 is available from NATEC, Behringstrasse 154, Postfach 501568, 2000 Hamburg 50, Germany.

a notifier should consult with the FDA concerning use of an appropriate fatty-food simulant before performing migration experiments.

The simulant volume should ideally reflect the volume-to-specimen surface area ratio expected to be encountered in actual food packaging. A ratio of 10 mL/in^2 is generally acceptable. Other ratios may be acceptable if migration levels do not approach concentrations reflecting the partition limit (i.e., the solubility of the FCS in the food simulant). Precipitation of the FCS from solution or a cloudy solution is an indication that this limit has been reached. The volume-to-surface area ratio should be reported.

d. *TEMPERATURE AND TIME OF TEST.* Notifiers should conduct migration testing under the most severe conditions of temperature and time anticipated for the proposed use. If the intended use of the food contact article involves contact with food at temperatures higher than room temperature, tests should be conducted at the highest use temperature for the maximum time period. In many instances, short time periods of elevated temperature-food contact are immediately followed by extended periods of storage at ambient temperatures. For such applications, FDA's recommended migration protocols call for short-term accelerated testing designed to simulate FCS migration that may occur during the entire food-contact scenario. Recommended protocols for selected situations are given in Appendix II; however, depending on the particular food-contact application, a specific protocol may be devised.

For room-temperature applications, a test temperature of 40°C (104°F) for 10 days is recommended. This accelerated testing protocol is based on studies showing that experimental migration levels were roughly equivalent to levels obtained after extended storage (6-12 months) at 20°C (68°F)[6].

For refrigerated or frozen food applications, the recommended test temperature is 20°C (68°F).

For polymers, such as polyolefins, that are used with food at temperatures above their glass transition temperatures (i.e., the polymer is in the rubbery state), the highest migration values (typically, but not always, the ten day values) are used by FDA to calculate the concentration of migrants in food.

Polymers such as polyethylene terephthalate (PET) and polystyrene (PS), however, are used with food at temperatures below their glass transition temperatures (i.e., the polymer is in the glassy state). At a fixed temperature, the rate of diffusion of migrants through a polymer in the glassy state is lower than if the polymer were in the rubbery state. For this reason, accelerated testing for 10 days at 40°C might underestimate migration that would occur during the entire food-contact scenario. Therefore, migration data obtained over ten days at 40°C should be extrapolated to 30 days in order to better approximate migration levels expected after extended time periods at ambient conditions. The notifier may carry out testing for 30 days to avoid uncertainties in extrapolation. If a notifier provides data that demonstrate that a different

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[6] Previous test protocols (prior to 1995) recommended a test temperature of 49°F for 10 days. Recent studies by FDA, however, have shown little difference in migration levels at 49°C and 40°C (104°F). Furthermore, the differences in migration levels between 49°C and 40°C are of even less significance for migration studies requiring elevated temperatures (e.g., 100°C or 121°C) for the first two hours. Up to 80% of the total migration observed over the 10 day period is usually completed within this two hour period at the higher temperature. Therefore, 40°C is regarded as acceptable for migration studies for room-temperature applications and for the portion of the migration test for elevated-temperature applications intended to reflect long term ambient storage.

extrapolation period is more appropriate for a given adjuvant/polymer combination, such information may be used for evaluating exposure.

For restricted uses where the maximum shelf life and food-contact temperature of an article are known, the notifier is encouraged to carry out migration studies for the maximum shelf life under temperature conditions approximating expected use. Notifiers may want to consult FDA before undertaking such tests.

For each migration experiment FDA recommends that portions of the test solutions be analyzed during at least four time intervals. Recommended sampling times for a ten-day test are 2, 24, 96, and 240 hours. FDA recommends that notifiers analyze a blank or control using a test cell identical to that used for the test article.

e. *END TESTS.* It is important for notifiers to realize that the appropriate migration test conditions for a new FCS are not those described in §175.300, §176.170 or other sections in 21 CFR. These published "end-test" extractions are quality control test methods that are used to verify whether a particular product is equivalent to the material that served as the basis for the regulation. End tests bear no relation to the migration testing recommended for evaluating probable exposure to a new FCS and may not be used to support notification of an FCS.

2. Characterization of Test Solutions & Data Reporting

Notifiers should perform migration studies in triplicate and analyze the test solutions for the migrants. If the PMN is for a polymer, the notifier should determine the amount and nature of total nonvolatile extractives (TNEs). Ordinarily, the TNEs are determined gravimetrically. The nature of the extractives, which may include monomers, oligomers, adjuvants, and catalyst residues, is determined by suitable chemical or physical tests, such as NMR, UV-visible, and atomic absorption spectroscopy, mass spectrometry, and gas or liquid chromatography. The notifier should indicate the limit of quantitation and selectivity of the methods used. If quantitation of individual migrants is not possible, the notifier should determine the distribution of the extractives between organic and inorganic fractions by solvent fractionation (i.e., the fraction of the TNE residue that is soluble in chloroform). This serves, as a first step, to focus on the migrants of interest (e.g., organic components) in determining exposure estimates. In these instances, FDA generally will estimate exposure to TNEs from the use of the FCS assuming that the TNEs (or chloroform-soluble TNEs) consist solely of low molecular weight oligomers that are chemically equivalent. Because the degree of toxicological testing depends on the magnitude of the exposure estimate, it should be to the notifier's advantage to quantitate the components in the TNEs that are not chemically equivalent (e.g., differentiate between low molecular weight oligomers and polymer adjuvants).

Test solutions from polymers that are the subject of a PMN should also be analyzed for constituent monomers. Alternatively, the known residual monomer level in the polymer may be used to calculate monomer dietary concentrations by using the density of the polymer, the maximum anticipated thickness of the food contact article, and by assuming that all of the residual monomer migrates into food and that ten grams of food contact one square inch of food-contact article.

If the PMN is for a polymer adjuvant, FDA normally recommends that the test solutions be analyzed only for the adjuvant. Occasionally, however, it may be necessary to quantitate, in the test solutions, impurities or decomposition products present in the adjuvant if they might be expected to become components of the daily diet in toxicologically significant quantities. A common example would be the presence of carcinogenic impurities in the adjuvant.

It may also be necessary to quantitate, in the test solutions, decomposition products produced (a) as a result of the FCS exhibiting its intended technical effect in the food contact article, or (b) in the test solutions after migration of the FCS. An example would be the use of a new antioxidant for polyolefins. Polymer antioxidants, by their very nature, would be expected to partially decompose during thermal processing of the resin or food-contact article containing the substance. Frequently, decomposition also occurs after migration of the FCS into food or food simulant, where temperatures may reach 120°C with fatty-food simulants. Information on decomposition in the food simulants may be obtained by conducting stability studies on the FCS in parallel with the migration studies.

Notifiers should report results in terms of milligrams of substance extracted per square inch (mg/in^2) of surface area. Migration amounts are often expressed in terms of mg/dm^2. The mixed unit mg/in^2 is preferred, however, to facilitate conversion to concentration in food. If ten grams of food are in contact with one square inch of packaging surface, a migration of 0.01 mg/in^2 corresponds to a concentration in food of 1 mg/kg. For specialized food-contact applications where an assumed ratio of 10 g food per in^2 is not appropriate, such as in dual-ovenable trays and microwave heat-susceptor applications, notifiers should use the lowest ratio from the actual food-contact applications and provide justification for the ratio selected.

3. Analytical Methods

Notifiers should submit the following for each method:

a. *DESCRIPTION OF THE METHOD.* A detailed description that can be followed by an experienced analytical chemist. The description should include discussions on the procedure's accuracy, precision, selectivity, limit of quantitation (LOQ), and limit of detection (LOD)[7]. If a literature reference is available, a copy should be included in the PMN.

b. *STANDARD CURVES.* Standard curves or calibration curves obtained by analyzing a prepared medium fortified with several known amounts of analyte to obtain concentrations both greater than, and less than, the concentration of migrant in the test solutions. The prepared medium may be the pure solvent, a solution of known ionic strength, etc. The data points from which the standard curve is derived should bracket the concentration of the migrant in the test solution. An analyte concentration of 1 mg/kg determined from a standard curve obtained from concentrations of 10, 15 and 20 mg/kg would generally be unacceptable. The

[7] The LOD is the lowest concentration of analyte that the analytical method can reliably detect above a blank (or control). It is preferable that the LOD be determined from analyses of five blank samples. The blank signal (i.e., the analyte response for the blank sample or the width of the baseline close to the actual or expected analyte peak) is measured, and the average signal and standard deviation for the blank are calculated. The signal corresponding to the LOD is located three standard deviations above the average blank signal. The blank signal for the LOD is usually determined from the peak-to-peak noise measured on the baseline close to the actual or expected analyte signal. See American Society for Testing and Materials (ASTM), E 1303-95, or ASTM E 1511-95.

The region for quantitation of the analyte should clearly be above the LOD. The signal corresponding to the LOQ is located ten standard deviations above the average blank signal. See Currie, 1968) and (Keith, et al., 1980).

correlation coefficient and standard errors of the Y intercept and the slope should be reported with the standard curve.

c. *EXAMPLES OF SPECTRA OR CHROMATOGRAMS.* Sample spectra and chromatograms, clearly identifying and labeling all major peaks to avoid ambiguities in interpretation.

d. *EXAMPLE CALCULATIONS* Example calculations relating the data obtained from instrumental methods to the reported levels (preferably in milligrams migrants per square inch of sample surface area) provide the reviewer with an internal check on the reported method.

e. *VALIDATION OF ANALYTICAL METHODS.* Validation of a method's intended use, the determination of accuracy and precision, usually involves: 1) replicate analyses of appropriate matrices fortified with known amounts of the analyte, at concentrations similar to those encountered in the migration studies, and 2) determination of the percentage recovery of the fortified analyte. In cases where a polymer adjuvant is the subject of interest, test solutions of the polymer formulated without the adjuvant may serve as the matrix for fortification and recovery measurements. Recovery is defined as the difference between measured analyte levels in the fortified and unfortified matrices. Percent recovery is the recovery divided by the fortified level times 100, i.e., if "a" is the measured level in the unfortified solution, "b" is the measured level in the fortified solution and "c" is the fortification level, then percent recovery equals (b-a)/c x 100.

If migration test solutions are fortified, they should be fortified before analytical workup but after the prescribed test time, e.g., 240 hours. FDA recommends that the actual test solutions be fortified and not the pure food simulants. Fortification of pure simulants instead of the test simulants is probably the most common deficiency in the validation section of an analytical method.

The notifier should perform fortification and recovery experiments using three (3) sets of triplicate samples of the test simulants with each set fortified at a separate level. The fortification levels should be one-half (½), one (1), and two (2) times the measured concentration of the analyte in the food simulant. In the event that the FCS is not detected, the notifier should determine the LOD for the method. For quantifiable levels of the analyte, acceptable recoveries should meet the following criteria:

Levels in food or food simulants[a]	Acceptable average recovery	Acceptable relative standard deviation
<0.1 mg/kg	60-110%	<20%
>0.1 mg/kg	80-110%	<10%

a- If 0.001 mg of a substance is extracted from one square inch of packaging material into 10 grams of food or food simulant, the estimated concentration in food is 0.1 mg/kg.

In evaluating the precision of the analytical method, the variability arising from analyses of individual samples can be eliminated by performing triplicate analyses on a homogeneous composite (a blend of the triplicate samples) where practicable.

Other validation procedures may be appropriate depending on the particular analysis. For example, analysis of the same test solution by two independent analytical methods would be acceptable validation. Similarly, the method of standard additions is an acceptable alternative in certain cases, such as metal analysis by atomic absorption spectroscopy. In this case, the notifier should fortify the matrix at two separate concentrations (at least) in addition to the unfortified concentration, and verify the linearity of the standard addition curve by calculation of the least squares correlation coefficient (r should be ≥ 0.995).

The notifier should submit representative spectra or chromatograms from validation analyses of fortified and blank samples. Spectra or chromatograms of the "blank" should be submitted to facilitate the verification of the absence of interferences. An illustrative example appears in Appendix III.

4. Migration Database

Migration data for specific migrant/polymer/food simulant systems at given temperatures that exhibit a predictable migration-time behavior, e.g., Fickian diffusion, may be used to predict migration at other temperatures. Thus, the need for migration studies for new applications, which in certain cases such as high temperature applications may be difficult to perform, may be reduced.

For example, migration data obtained over 10 days (240 h) at 40°C that exhibits Fickian behavior, in combination with migration data obtained at other temperatures (e.g., 60°C and 80°C), may be extrapolated by means of an Arrhenius plot to predict migration under retort conditions (121°C/2 h and 40°C/238 h), if no apparent change in polymer morphology, such as glass transition or polymer melting, is expected between 30°C and 130°C. Apparent diffusion coefficients, D, at 121°C for each migrant/polymer/food simulant can be obtained from a plot of ln D vs 1/T(K). Thus, migration for 2 hours at 121°C can be estimated and added to migration after 238 hours at 40°C to obtain total migration expected for retort and ambient storage conditions. The density and thickness of the polymer sample and initial concentration of the migrant in the polymer are also necessary for the calculations.

The FDA Migration Database is intended as a resource for migration data, including diffusion coefficients and relevant polymer/additive properties. FDA continues to compile migration data from various sources for use in estimating migration levels for FCSs. Reliable migration data, e.g., data that follow Fickian diffusion, submitted in support of a PMN would be added to the database. In addition, only migration levels that have been measured at three or more time intervals for a given temperature will be considered for inclusion in the migration database. Notifiers may submit suitable data for inclusion into the database in the form of a letter, as part of a notification, or in a Food Additive Master File. The FDA migration database (hardcopy) is available through the Freedom of Information Act (FOIA) (also see the CFSAN website at http://www.vm.cfsan.fda.gov/~dms.foia.html).

5. <u>Migration Modeling</u>

FDA recommends that a notifier submit relevant and reliable data on an FCS for use in estimating migration levels in food and, in turn, potential consumer exposure. As discussed above, migration levels in food are typically estimated based on the results of migration testing under the anticipated conditions of use or, in certain cases, under the assumption of 100% migration of the FCS to food. These two approaches are adequate in most instances.

A third alternative involves migration modeling. One simple approach to modeling migration for *specific* migrant/polymer/food simulant systems, based on select experimental data, was discussed above in Section II.D.4. However, the mathematical modeling of migration using the basic principles of diffusion has not found widespread application, largely due to the lack of necessary material constants such as diffusion coefficients. Diffusion coefficients may often be found in the open literature or the FDA migration database. In all cases, the source of any material constants used in migration modeling should be appropriately referenced.

Recently, however, semi-empirical methods have been developed to determine migration levels with limited or, in certain cases, no migration data (see, e.g.,(Limm and Hollifield, 1996) and (Baner, et al., 1996). These diffusion models rely on estimation of diffusion coefficients based on the nature of the migrant and the physical properties of the polymer. They may be useful substitutes for, or additions to, experimental data under limited circumstances. Several caveats should be considered in the application of such diffusion models. First, distribution of the migrant in the polymer is considered isotropic. Non-isotropic distribution, whether intentional or unintentional, would be expected to result in non-Fickian migration. Two, other aspects of migration, such as partitioning, mass transfer, polymer morphology, shape/polarity of the migrant, and plastization of the polymer, are not considered in these models. These factors should be carefully considered when deriving migration levels to food using modeling techniques.

E. CONSUMER EXPOSURE

Migration data developed using the procedures outlined in Section II. D. are intended to provide estimates of the highest level of migration to food that might result from the anticipated use of the FCS. FDA estimates probable exposure to the FCS by combining the migration data with information on uses of food-contact articles that may contain the FCS (i.e., on the fraction of a person's diet likely to contact packaging materials containing the FCS).

From a given concentration of the FCS in the daily diet, the estimated daily intake (EDI) is calculated as the product of that concentration and the total food intake, assumed to be 3000 grams per person per day (solids and liquids). A concentration in the daily diet of 1 ppm corresponds to an EDI of 1×10^{-6} g FCS/g food x 3000 g food/person/day or 3 mg/person/day.

Both the concentration in the daily diet and the EDI from the subject PMN and the cumulative EDI (CEDI) from all regulated uses and effective PMNs are used by FDA in the safety evaluation of an FCS. The CEDI the FCS should be used in determining the types of toxicity studies used to establish safety under the proposed conditions of use. Toxicological data recommendations for several tiers of CEDIs resulting from all proposed and permitted uses of the FCS, including regulated uses, uses that were the subject of previous PMNs, and the use in the subject

PMN, are described in the document entitled "Preparation of Premarket Notifications for Food Contact Substances: Toxicology Recommendations".

1. Calculation of Exposure

a. *CONSUMPTION FACTOR*. The term "Consumption Factor" (CF) is used to describe the fraction of the daily diet expected to contact specific packaging materials. The CF represents the ratio of the weight of all food contacting a specific packaging material to the weight of all food packaged. CF values for both packaging categories (e.g., metal, glass, polymer and paper) and specific food-contact polymers are summarized in Table I of Appendix IV. These values were derived using information on the types of food consumed, the types of food contacting each packaging surface, the number of food packaging units in each food packaging category, the distribution of container sizes, and the ratio of the weight of food packaged to the weight of the package. These values may, however, be modified as new packaging information is received. Several of the values contained in Table I of Appendix IV have been updated since the 1995 document entitled "Recommendations for Chemistry Data for Indirect Food Additive Petitions."

When FDA computes exposure to an FCS, the Agency assumes that the FCS will capture the entire market for which it is intended for use. This approach reflects both uncertainties about likely market penetration as well as limitations in the data surveyed. Thus, if a company proposes the use of an antioxidant in polystyrene, it is assumed that the antioxidant will be used in all polystyrene manufactured for food contact. In certain cases where an adjuvant is intended for use in only a part of a packaging or resin category, a lower CF representing the coverage that is sought may be used. For example, if a stabilizer is intended for use only in rigid and semirigid polyvinyl chloride (PVC), a CF of 0.05 rather than 0.1 could be used in estimating exposure since only about 50% of all food-contact PVC could contain the stabilizer. Another example is the division of polystyrene into impact and non-impact categories (see Table 1, Appendix IV). In order to reduce conservatisms, notifiers are encouraged to submit as detailed information as possible on the anticipated resin or packaging market(s) that may be captured by articles manufactured from the FCS.

When new products are introduced, they will initially be treated as replacement items for existing technology. FDA generally makes estimates based on the assumption that the new product will capture the entire market. For example, the retortable pouch was initially treated as a replacement for coated metal cans and was assigned a CF of 0.17. As additional information on actual use of the retortable pouch became available, the CF was lowered to 0.05. In certain cases, the submission of resin or packaging market data may lead to the use of a lower CF.

b. *FOOD-TYPE DISTRIBUTION FACTOR*. Before migration levels can be combined with CF values to derive estimates of probable consumption, the nature of the food that will likely contact the packaging material must be known. Migration into a fatty-food simulant, for example, will be of little use in estimating probable exposure if the packaging material is used exclusively to package aqueous food. To account for the variable nature of food contacting each packaging material, "food-type distribution factors" (f_T) have been calculated for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic and fatty. Appropriate f_T values for both packaging categories and polymer types appear in Table II of Appendix IV.

c. *CONCENTRATION IN THE DAILY DIET AND EDI*. FDA recommends the following approach for calculating the concentration of the FCS in the daily diet. The concentration of the FCS in food contacting the packaging material, <M>, is derived by multiplying the appropriate f_T values by the migration values,

M_i, for simulants representing the four food types. This, in effect, scales the migration value from each simulant according to the actual fraction of food of each type that will contact the packaging material.

$$\langle M \rangle = f_{\text{aqueous and acidic}}(M_{10\%\ \text{Ethanol}})+f_{\text{alcohol}}\ (M_{50\%\ \text{Ethanol}})+f_{\text{fatty}}(M_{\text{fatty}})$$

where M_{fatty} refers to migration into a food oil or other appropriate fatty-food simulant.

The concentration of the FCS in the diet is obtained by multiplying <M> by CF. The EDI is then determined by multiplying the dietary concentration by the total weight of food consumed by an individual per day. FDA assumes that an individual consumes 3 kg of food (solid and liquid) per day (see Appendix IV for sample calculations):

$$\text{EDI} = 3\ \text{kg food/person/day} \times \langle M \rangle \times \text{CF}$$

d. *CUMULATIVE EXPOSURE.* If the FCS that is the subject of a PMN is already regulated for other uses in 21 CFR 170-199, or has been the subject of previous effective PMNs, FDA generally estimates the cumulative exposure to the FCS from the proposed and permitted uses (see the example in Appendix IV). Information on the regulatory status of an FCS may be obtained by inspection of 21 CFR 170-199, searching the CFR on the Government Printing Office (GPO) World Wide Website at htpp:/www.access.gpo.gov/nara/cfr/index.html, or contacting FDA directly. Information on effective PMNs for an FCS may be obtained through the FDA website or by contacting FDA directly. An estimate of cumulative exposure for the regulated and notified uses of an FCS can be obtained by contacting FDA. FDA also maintains a database of cumulative EDIs for food contact substances on the agency's internet site.

The approach outlined above is designed to deal with the majority of FCSs intended for single-use. For estimating dietary exposures to components of repeat-use items and articles used in or with food processing equipment, exposure estimates will also consider estimates of the amount of food to be contacted during the service life of the food-contact article (see Appendix II, Section 4).

2. Exposure Refinement

Exposure estimates will, in general, be made using the aforementioned procedures. More refined exposure estimates may be possible, however, with additional information provided in a PMN. For instance, subdividing packaging or resin categories could reduce the calculated exposure by lowering the CF for the category. The division of PVC into rigid and plasticized categories and PS into impact and non-impact categories, cited above, are two examples. Another example is the division of polymer coatings for paper into subcategories, such as poly(vinyl acetate) coatings, styrene-butadiene coatings, etc. If an FCS is to be used solely in styrene-butadiene coatings for paper, use of the CF for polymer-coated paper (0.2, Appendix IV, Table 1), would be a gross exaggeration. As noted above, FDA encourages the submission of marketing information that may be used to subdivide the packaging market(s) anticipated for articles manufactured from the FCS.

In those cases where the nature of the coverage requested may necessitate more detailed information or where a notifier believes that exposure will be overstated by simply selecting CF and f_T values presented in Appendix IV, data of the following type may be submitted to facilitate calculations of CF and f_T values for materials likely to contain the FCS:

a. Estimates of the total amount of food in contact with the packaging material determined using either:

(1) package unit data (number of units and their size distribution), or

(2) pounds of packaging material produced for food contact, container size distribution, and ratios of weight of food packaged to weight of package.

b. Characterization of the foods that might contact the food package, along with supporting documentation, and the likely f_T values.

c. Information that would demonstrate that only a fraction of a packaging or resin category would be affected by the coverage sought.

d. Technological limitations that could affect the type of food contacted or the fraction of the diet that might be contacted.

APPENDIX I

FATTY-FOOD SIMULANTS FOR SPECIFIC POLYMERS

A food oil is the most extreme example of a fatty food. If contact with fatty foods is anticipated, FDA recommends that a notifier conduct migration studies using a food oil as the food simulant. In addition to food oils such as corn and olive oil for which extensive migration data already exist, the use of HB307 (a mixture of synthetic triglycerides, primarily C_{10}, C_{12}, and C_{14}) as a fatty-food simulant has previously been recommended. Studies in FDA laboratories have shown that Miglyol 812, a fractionated coconut oil having a boiling range of 240-270°C and composed of saturated C_8 (50-65%) and C_{10} (30-45%) triglycerides, is also an acceptable alternative. Since use of these oils for FCS migration may not always be practicable, the use of aqueous-based solvents that simulate the action of these liquid fats is sometimes necessary. While it seems unlikely that one solvent will be found that simulates the action of a food oil for all food-contact polymers, the following list presents polymers for which adequate data exist to support the use of aqueous-based solvents as fatty-food simulants. The recommendation for the use of these solvents is based upon studies done at FDA, at the National Institute of Standards and Technology (formerly The National Bureau of Standards), and by Arthur D. Little, Inc. under contract to FDA. (A list of general references pertaining to these studies is shown in Appendix V.) For polymers other than those listed below, notifiers should consult FDA before undertaking any migration experiments.

1. Polyolefins complying with §177.1520 and ethylene-vinyl acetate copolymers complying with §177.1350 .... 95% or absolute ethanol
2. Rigid poly(vinyl chloride) .... 50% ethanol
3. Polystyrene and rubber-modified polystyrene .... 50% ethanol
4. Poly(ethylene terephthalate) .... 50% ethanol

Absolute or 95% ethanol has been found to be an effective fatty-food simulant for polyolefins; however, it appears to exaggerate migration for other food-contact polymers.

Previous test protocols (prior to 1988) recommended the use of heptane as a fatty-food simulant. To account for the aggressive nature of heptane relative to a food oil, division of migration values by a factor of five was permitted. Studies have shown, however, that the exaggerative effect of heptane relative to a food oil varies over orders of magnitude depending on the polymer extracted. Thus, heptane is no longer recommended as a fatty-food simulant. However, we recognize that in cases where very low migration is anticipated, such as for inorganic adjuvants or certain highly cross-linked polymers, heptane can be useful due to the ease of analytical workup. Because of the known variance in the exaggerative effect of heptane relative to food oil, if heptane is used, migration values will generally not be divided by any factor unless there is adequate justification.

APPENDIX II

SELECTED MIGRATION TESTING PROTOCOLS

The following migration testing protocols are intended to simulate most anticipated end-use conditions of food-contact articles. These protocols are based on the premise that migration to aqueous- and fatty-based foods is typically diffusion-controlled within the polymer, strongly affected by the temperatures encountered during food contact, and further modified by the solubility of the FCS in the foods. Therefore, migration testing with food simulants at the highest temperatures to be experienced by the package during food contact is recommended. Testing with actual fatty foods is also an option, although determination of the analytes of interest is often very difficult. In those instances where the expected use conditions are not adequately simulated by these protocols or testing with food simulants at the highest anticipated food-contact temperature is not practical, alternatives to those protocols presented below should be developed in consultation with FDA.

1. General Protocols (Single-Use Applications) Corresponding to Condition of Use

As noted in Appendix I, migration to fatty foods is evaluated using a fatty food, a pure liquid fat, or, alternatively, aqueous ethanol solutions when analytical limitations preclude sensitive analyses. As noted in Section II.D.1.c, migration to aqueous, acidic, and low-alcoholic foods is generally evaluated using 10% ethanol and migration to high-alcohol foods is generally evaluated using 50% ethanol.

The migration protocols given below are intended to model thermal treatment and extended storage conditions for polymers, such as polyolefins, used with food at temperatures above their glass transition temperatures. The extended storage period generally involves testing at 40°C for 240 hours (10 days). As discussed in Section II.D.1.d, migration data obtained at 10 days for polymers used below their glass transitions temperature should be extrapolated to 30 days to better approximate migration levels expected after extended storage at ambient conditions.

FDA recommends the following approaches:

A. *High temperature, heat sterilized or retorted above 100°C (212°F).*

10% Ethanol[a] .... 121°C (250°F) for two hours

50% Ethanol .... 71°C (160°F) for two hours

Food Oil (e.g., corn oil) or HB307
or Miglyol 812 .... 121°C (250°F) for two hours
or
50% or 95% Ethanol[a,b] .... 121°C (250°F) for two hours

a- Requires a pressure cell or autoclave, see Appendix V. Appropriate safety precautions should be exercised when using equipment generating pressures above 1 atmosphere.
b- Depends on food-contact layer, see Appendix I.

After two hours at elevated temperatures, continue the tests at 40°C (104°F) for 238 hours to a total of 240 hours (10 days). Analyze the test solutions at the end of the initial two hour period, and after 24, 96 and 240 hours.

B. *Boiling water sterilized.* The recommended protocol is the same as for Condition of Use A except that the highest test temperature is 100°C (212°F).

C. *Hot filled or pasteurized above 66°C (150°F).* Add solvents to the test samples at 100°C (212°F), hold for 30 minutes, and then allow to cool to 40°C (104°F). Maintain the test cells at 40°C (104°F) for ten days with samples taken for analysis after the intervals indicated for the previous protocols. If the maximum hot fill temperature will be lower than 100°C (212°F), test solvents may be added at this lower temperature. Alternatively, perform migration studies for 2 hours at 66°C (150°F) followed by 238 hours at 40°C (104°F). For the alternative method, the longer time at the lower temperature (2 hours at 66°C vs 30 minutes at 100°C) compensates for the shorter time at 100°C.

D. *Hot filled or pasteurized below 66°C (150°F).* The recommended protocol is analogous to that for C except that all test solvents are added to the test samples at 66°C (150°F) and held for 30 minutes before cooling to 40°C (104°F).

E. *Room temperature filled and stored (no thermal treatment in the container).* The notifier should conduct migration studies for 240 hours at 40°C (104°F). Analyze the test solutions after 24, 48, 120 and 240 hours.

F. *Refrigerated storage (no thermal treatment in the container).* The recommended protocol is identical to that for E except that the test temperature is 20°C (68°F).

G. *Frozen storage (no thermal treatment in the container).* The recommended protocol is identical to F except that the test time is five (5) days.

H. *Frozen or refrigerated storage; ready-prepared foods intended to be reheated in container at time of use:*

10% Ethanol[a] .... 100°C (212°F) for two hours

Food Oil (e.g., corn oil) or HB307
or Miglyol 812™ .... 100°C (212°F) for two hours
or
50% or 95% Ethanol[a,b] .... 100°C (212°F) for two hours

a- Requires a pressure cell or autoclave, see Appendix V.
b- Depends on food-contact layer, see Appendix I.

Applications involving the heating and cooking of food at temperatures exceeding 121°C (250°F) are not included under conditions of use A-H. Migration testing protocols for these applications are discussed in Section 11 of this Appendix.

2. <u>Adjuvants for Polyolefins</u>

In general, under identical testing conditions, levels of migrants from low-density polyethylene (LDPE) are higher than from high-density polyethylene (HDPE) or polypropylene (PP). Migration studies done solely on LDPE (complying with §177.1520(a)(2)) at 100°C (approximately the highest temperature at which LDPE remains functional) are, therefore, generally sufficient to provide coverage for all polyolefins including PP, which may be used for retort applications. In such a case, the CF for all polyolefins (CF = 0.33) generally will be used instead of the individual CF for LDPE (see Appendix IV, Table I). Levels of migrants from HDPE are generally higher than from PP. Thus, migration studies conducted with HDPE are generally adequate to permit coverage in PP under the same conditions of use. In such a case, the combined CF of PP and HDPE will be used in deriving exposure estimates. However, when seeking coverage for all polyolefins it is usually advantageous to perform migration testing on HDPE, PP and LLDPE, complying with §177.1520, as well as LDPE. By doing this, actual migration values for these polyolefins, which will likely be lower that those obtained from LDPE, may be used to calculate the EDI.

3. Adjuvants for Polymers (other than Polyolefins)
   Adjuvants for More than One Polymer

The migration testing protocols for polymers other than polyolefins are the same as those in Section 1 of this Appendix. Consult Appendix I for the recommended fatty-food simulant.

If use of an FCS is sought without limitation to specific polymers, the notifier may obtain approval of this broad coverage by testing with an unoriented LDPE sample complying with § 177.1520(a)(2). The test protocol depends on the anticipated conditions of use (refer to Section 1 of this Appendix). If the most rigorous applications correspond to Condition of Use A (Section 1.A), the test temperature should be the highest temperature at which the polymer remains functional (ca. 100°C for LDPE). The CF for all polymers (Appendix IV, Table I, CF = 0.8) should be used with the migration data to calculate the concentration of the FCS in the daily diet. In general, a lower calculated concentration in the daily diet will result if a series of representative polymers are separately tested and individual consumption factors are applied (refer to the examples in Appendix IV). A notifier should consult with FDA to determine which representative polymers should be tested.

4. Articles Intended for Repeated Use

A notifier should test the article with 10% and 50% ethanol and a food oil (e.g., corn oil) or other fatty-food simulant (e.g., HB307 or Miglyol 812) for 240 hours at the highest intended temperature of use. The test solutions should be analyzed for migration of the FCS after 8, 72, and 240 hours. Notifiers should provide estimates of the weight of food contacting a known area of repeat-use article in a given time period as well as an estimate of the average lifetime of the article. Together with the migration data, this will allow calculation of migration to all the food processed over the service life of the article.

In the case of an adjuvant in a repeat-use article, FDA strongly recommends an initial calculation of a "worst case" level in food by assuming 100% migration of the adjuvant over the service life of the article and dividing that value by the quantity of food processed. If this calculated concentration is sufficiently low, migration studies will be unnecessary.

5. Coatings for Cans

The migration testing protocol is usually that outlined in Section 1.A of this appendix for high temperature, heat sterilized or retorted products. If broad coverage is sought for all types of coatings, the notifier should consult with FDA to determine which coatings should be tested. For use conditions less severe than retort sterilization at 121°C, notifiers should follow the migration test protocols outlined in Sections 1.B-G of this appendix which most closely approximate the most severe expected use conditions.

6. Uncoated & Clay-Coated Papers with Latex Binders

These papers are intended for contact with food at temperatures less than 40°C for short periods of time. The FDA recommended protocol is the following:

10% Ethanol .... 40°C (104°F) for 24 hours

50% Ethanol .... 40°C (104°F) for 24 hours
or
Food Oil (e.g., corn oil) or HB307 or Miglyol 812 .... 40°C (104°F) for 24 hours

Migration studies conducted on uncoated or clay-coated papers typically result in a high level of extractives due to the large number of low-molecular weight, soluble components in both paper and paper coatings. Therefore, when total nonvolatile or chloroform-soluble total nonvolatile extractives are determined for a paper coating, FDA recommends that the corresponding extractives should not be subtracted from uncoated paper as a blank correction. Rather than using paper as a support for the coating, it is often useful to apply the coating to a suitable inert substrate, such as glass or metal, for use in migration testing. For a new adjuvant in paper coatings, FDA recommends the analysis of the test solutions for the unregulated adjuvant. For a new polymer used in paper coatings, FDA recommends the analysis of the test solutions for constituent oligomers and monomers.

7. Specially Treated Papers

This class includes such types as fluoropolymer- and silicone-treated papers that have oil-resisting and heat-resisting properties. The specific protocol depends on the particular uses anticipated. It is recommended that the notifier either devise a protocol and submit it to FDA for comment or request comment from FDA about appropriate test conditions.

8. Adhesives (Room temperature or below)

In previous chemistry documents for indirect additives, migration tests were not recommended for adhesives intended for use at room temperature or below and in accordance with §175.105. (High temperature applications are discussed in Section 9). This recommendation was based on consideration of subparagraph (a)(2) of §175.105 which specifies that the adhesive is either separated from food by a functional barrier, or the quantity of adhesive that contacts aqueous and fatty food is limited to the trace amount at seams and edges.
If a notifier proposes to use the adhesive or adhesive component in concordance with the limitations of §175.105, migration levels for the notified substances will generally be assumed to be no greater than 50 ppb, as is the case for petitioned adhesives components. Applying a CF of 0.14 for adhesives gives a dietary concentration of 7 ppb. If the assumptions of §175.105 cannot be supported, notifiers should submit data or calculations to model the intended use of any adhesive component. If a notifier wishes to perform migration testing, multilaminate samples should be fabricated with the maximum anticipated amount of the adhesive component and with the minimum thickness of the food contact layer. The migration protocol corresponds to condition of use E. Alternatively, migration levels in food can be estimated based on migration modeling (see Section II.D.5).

9. Laminates & Coextrusions

Components of multilayer structures used above room temperature are the subject of two regulations. One covers laminates used in the temperature range 120°F (49°C)-250°F (121°C) (21 CFR 177.1395) and the other covers laminate structures used at temperatures of 250°F (121°C) and above (21 CFR 177.1390). Layers not separated from food by barriers preventing migration during expected use must be listed in these regulations, or be the subject of an effective PMN, unless they are authorized elsewhere for the intended use conditions as specified in 21 CFR 177.1395(b)(2) and 21 CFR 177.1390(c)(1). Test protocols presented in Sections 1.A-H may be appropriate for evaluating the level of migration from non-food-contact layers of some laminate structures. End uses that differ considerably from those considered in these Guidelines, however, should be the subject of special protocol development in consultation with FDA.

10. Boil-In-Bags

FDA recommends the protocol employed in Condition of Use C.

11. Special High-Temperature Applications

Advances in packaging technology have led to the development of food packaging materials that can withstand temperatures substantially exceeding 121°C (250°F) for short periods of time for the purposes of heating and cooking of ready-prepared food. FDA recommends use of the following protocols for migration testing of dual-ovenable containers and microwave heat susceptor materials.

a. DUAL-OVENABLE TRAYS

For high temperature oven use (conventional and microwave), FDA recommends migration testing at the maximum intended conventional oven cooking temperature for the longest intended cooking time, using a food oil, or a fatty-food simulant such as Miglyol 812.

b. MICROWAVEABLE CONTAINERS

The temperature ultimately experienced by a food-contact material when cooking foods in a microwave oven is dependent on many factors. Some of these are food composition, heating time, mass and shape of the food, and shape of the container. For example, food with mass in excess of 5 g/in^2 container surface area and having a thick shape will require longer cooking times to achieve the desired degree of interior cooking than if it had a lower mass-to-surface area ratio and were thinner. Because the ultimate temperature of the container will depend on many factors and is, therefore, not readily predicted, it is recommended that notifiers consult with FDA on any planned testing protocol prior to initiating migration testing.

c. MICROWAVE HEAT-SUSCEPTOR PACKAGING

The high temperatures attained by packaging using susceptor technology may result in (a) the formation of significant numbers of volatile chemicals from the susceptor components and (b) loss of barrier properties of food-contact materials leading to rapid transfer of nonvolatile adjuvants to foods. Studies by FDA, with hot vegetable oil in contact with a susceptor, have shown that the susceptor materials liberate volatile chemicals that may be retained in the oil at parts-per-billion (ppb) levels. FDA recommends the use of the protocol outlined by McNeal and Hollifield (McNeal and Hollifield, 1993) for the identification and quantification of *volatiles* from susceptors.

To isolate and identify the total available *nonvolatile* extractives, notifiers should perform Soxhlet extractions on finely shredded portions of laminated susceptor materials using polar and nonpolar solvents as outlined in Appendix X1 of ASTM method F1349-91. Migration protocols for *UV-absorbing nonvolatiles* are also outlined in ASTM method F1349-91 and in (Begley, and Hollifield, 1991). The ASTM method relies on the determination of a time-temperature profile based on cooking a food product according to label directions, for the maximum cooking time. The temperature reached by a microwave heat susceptor, however, is dependent on the amount and characteristics of the food product. Testing methods should involve a standard set of conditions that represent the maximum anticipated use conditions. Therefore, FDA recommends that migration studies be conducted in a manner similar to that outlined by Begley and Hollifield. The recommended standard test conditions are as follows:

1) use laminated susceptor stock representative of the proposed application(s);
2) use a microwave oven with an output wattage on the order of 700 watts;
3) use a maximum microwave time of 5 minutes;
4) use an oil mass-to-susceptor surface area on the order of 5 g/in^2; and
5) use a water load on the order of 5 g/in^2.

Exposure estimates may be based, in the absence of validated migration studies, on the assumption of 100% migration of the total nonvolatile extractives to food, as determined by Soxhlet extractions.

Validated migration protocols for the direct determination of aliphatic migrants are not available at this time. However, the amount of aliphatic migrants may be estimated by subtracting the UV-absorbing nonvolatiles and inert materials from the total nonvolatiles obtained by Soxhlet extraction (see Appendix X1 in ASTM method F1349-91). Exposure estimates for aliphatic migrants should be based on the assumption of 100% migration to food.

12. <u>Colorants for Plastics</u>

Some colorants, pigments in particular, may be quite insoluble in the food simulants 10%- and 95%- ethanol. In such cases, solubility information may provide a basis for an alternative to migration testing for evaluating worst-case exposure since migration levels would not be expected to exceed the limits of solubility of the colorant at the proposed use temperature. If the colorant is to be used in all plastic packaging, for which a CF = 0.05 would be used, a solubility below <u>ca.</u> 100 $\mu g/kg$ at 40°C would lead to a dietary concentration no greater than 5 ppb under conditions as severe as condition of use E. A solubility less than 10 $\mu g/kg$ would lead to an exposure below the threshold level of 0.5 ppb dietary concentration (See 21 CFR 170.39).

13. <u>Dry Foods with Surface Containing No Free Fat or Oil</u>
(21 CFR 176.170(c), Table 1, Food Type VIII)

Although studies have shown migration of certain adjuvants into dry foods (e.g., low molecular weight adjuvants in contact with porous or powdered foods), at the present time no migration testing is recommended.

14. <u>Wet-End Additives used in the Manufacture of Paper and Paperboard</u>

Paper additives used in the wet end of the papermaking process include those designed to improve the papermaking process, such as processing aids, and those designed to modify the properties of the paper, such as functional aids. Functional aids, mostly organic resins or inorganic fillers, are designed to bond to the paper fibers and, thus, are substantive to paper. For those FCSs that are substantive to paper, migration studies should be conducted and the test solutions analyzed for constituents of the substance. For example, in the case of a polymeric retention aid, the test solutions should be analyzed for constituent oligomers and monomers. On the other hand, processing aids are intended to remain with the process water slurry and, thus, are generally not substantive to paper. Exposure estimates for non-substantive additives may be based on migration studies, or alternatively, on scenarios involving partitioning of the additive between paper fibers and slurry water. The following example illustrates this approach:

> Consider an adjuvant added prior to the sheet-forming operation in the manufacture of paper. The intended use level is reported to be 10 mg/kg in the slurry. Since the additive is not substantive to paper, the mass of water (containing the additive) in contact with the pulp at the point in the papermaking process where the slurry enters the drier determines the level of the adjuvant retained in paper. Prior to entering the driers, the slurry is concentrated to contain approximately 33% pulp and 67% water. This corresponds to an adjuvant level of 20 mg/kg relative to the pulp. Assuming that finished paper contains 92% pulp, a paper basis weight of 50 mg/in^2, 100% migration of the adjuvant to food, and that 10 g of food contacts 1 in^2 paper, results in an adjuvant concentration in food is 0.09 mg/kg, or 90 μg/kg. Applying a CF of 0.1 for uncoated and clay-coated paper gives a dietary concentration of 9 ppb.

APPENDIX III

ILLUSTRATIVE EXAMPLE OF VALIDATION OF ANALYSES

Polyethylene film containing a new antioxidant was subjected to migration testing with 10% ethanol. The test solutions were analyzed for antioxidant migration. Tests were carried out in separate cells each containing 100 in^2 of film. Four sets of test solutions (in triplicate) were analyzed at 2, 24, 96 and 240 hours for a total of 12 test solutions. After each time interval, each solution from one set was evaporated to dryness, the residue dissolved in an appropriate organic solvent, and a known aliquot injected into a gas chromatograph.

Validation experiments are carried out with the set of test simulants exhibiting the highest level of antioxidant migration. To validate the analytical method, an additional three sets (in triplicate) using 10% ethanol can be run for 240 hours. Each set of these test solutions can then be fortified with the antioxidant at levels corresponding to one-half (½), one (1) and two (2) times, respectively, the average migration value determined for the regular (unfortified) 240 hour test solutions.

Instead, the notifier decided to carry out one large test using enough film and solvent for twelve analyses (three at each of the four time intervals). After 240 hours, the test solution was divided into twelve (12) equal solutions (i.e., four sets of triplicate samples). One set (three solutions) was found to contain antioxidant at an average level of 0.00080 mg/in^2. This value corresponds to 0.080 mg/kg in food if it is assumed that 10 grams of food contacts 1 in^2 of film. Of the remaining nine solutions (three sets), three solutions were fortified at concentrations corresponding to 0.00040 mg/in^2, three were fortified at 0.00080 mg/in^2 and three were fortified at 0.00160 mg/in^2. Each solution was worked up and analyzed as described above. To illustrate the recovery calculations, the results for the set of three solutions fortified at one-half times the average migration (0.00040 mg/in^2) are summarized in the following table:

Measured Level in each Sample (mg/in^2)[a]	Recovery (mg/in^2)[b]	Percent Recovery (%)[c]
0.00110	0.00030	75.0
0.00105	0.00025	62.5
0.00112	0.00032	85.0

a- includes 0.00040 mg/in^2 fortification.
b- calculated by subtracting the average level (0.00080 mg/in^2) from the measured levels in each sample.
c- calculated by dividing the recovery by the fortification level (0.00040 mg/in^2), and multiplying by 100 (see Section II.D.3.e).

The average percent recovery is 74.2%, and the relative standard deviation is 15.2%. These are within the limits specified (see Section I.D.3.e) for a concentration in food of 0.080 mg/kg (percent recovery 60-110%, relative standard deviation not exceeding 20%). If the corresponding percentages for the other two fortification levels are also within these limits, the validation for the 10% ethanol migration studies would be acceptable. The actual validation procedure used will, of course, depend on the particular type of analysis.

APPENDIX IV

CONSUMPTION FACTORS, FOOD-TYPE DISTRIBUTION FACTORS, AND EXAMPLE OF EXPOSURE ESTIMATE CALCULATIONS

This appendix summarizes packaging data recommended by FDA for evaluating exposure to FCS. An example of how these data are combined with levels of an FCS in food is also presented. A more complete discussion of the source of these data and their use in exposure calculations is presented in Section II.E.

TABLE I- CONSUMPTION FACTORS (CF)

Package Category	CF	Package Category	CF
A. General			
Glass	0.1	Adhesives	0.14
Metal- Polymer coated	0.17	Retort pouch	0.05
Metal- Uncoated	0.03	Microwave susceptor	0.01
Paper- Polymer coated	0.2		
Paper- Uncoated and clay-coated	0.1		
Polymer	0.4		
B. Polymer			
Polyolefins	0.35	PVC	0.1
LDPE	0.12	rigid	0.05
LLDPE	0.06	semirigid	0.05
HDPE	0.13	Polyester	0.05
PP	0.04	Cellophane	0.01
Polystyrene	0.1	Nylon	0.02
impact	0.04	Acrylics, phenolics, etc.	0.15
non-impact	0.06	EVA	0.02
		All Others[a]	0.05

[a]- As discussed in the text, a minimum CF of 0.05 will be used initially for all exposure estimates.

TABLE II- FOOD-TYPE DISTRIBUTION FACTORS (f_T)

Package Category	Food-Type Distribution (f_T)			
	Aqueous[a]	Acidic[a]	Alcoholic	Fatty
A. General				
Glass	0.08	0.36	0.47	0.09
Metal- Polymer coated	0.16	0.35	0.40	0.09
Metal- Uncoated	0.54	0.25	0.01[b]	0.20
Paper- Polymer coated	0.55	0.04	0.01[b]	0.40
Paper- Uncoated and clay-coated	0.57	0.01[b]	0.01[b]	0.41
Polymer	0.49	0.16	0.01[b]	0.34
B. Polymer				
Polyolefins,	0.67	0.01[b]	0.01[b]	0.31
Polystyrene	0.67	0.01[b]	0.01[b]	0.31
-impact	0.85	0.01[b]	0.04	0.10
-nonimpact	0.51	0.01	0.01	0.47
Acrylics, phenolics, etc.	0.17	0.40	0.31	0.12
PVC	0.01[b]	0.23	0.27	0.49
Acrylonitrile, ionomers, PVDC	0.01[b]	0.01[b]	0.01[b]	0.97
Polycarbonates	0.97	0.01[b]	0.01[b]	0.01[b]
Polyesters	0.01[b]	0.97	0.01[b]	0.01[b]
Polyamides (nylons)	0.10	0.10	0.05	0.75
EVA	0.30	0.28	0.28	0.14
Wax	0.47	0.01[b]	0.01[b]	0.51
Cellophane	0.05	0.01[b]	0.01[b]	0.93

[a]- For 10% ethanol as the food simulant for aqueous and acidic foods, the food-type distribution factors should be summed.

[b]- 1% or less

Examples of Exposure Estimate Calculations

The following hypothetical examples are intended to illustrate the calculation of the concentration of an FCS in the daily diet (CF x <M>, i.e., the fraction of food in the diet contacting the packaging material times the average concentration of the FCS in food) and its EDI.

Example 1

A PMN is received that describes the use of a new antioxidant at a maximum level of 0.25% w/w in polyolefins contacting food at or below room temperature (see Appendix II, Sections 1.E through 1.G). Migration values from LDPE reported to FDA for the three food simulants are given below:

Solvent (i)	M_i (mg/kg)
10% aqueous ethanol	0.060
50% aqueous ethanol	0.092
Miglyol 812	7.7

The notifier used a solvent volume-to-exposed surface area ratio of 10 mL/in^2. Therefore, solution concentrations are essentially equivalent to food concentrations (under the assumption that 10 g food contacts 1 in^2 of surface area). The CF and f_Ts for polyolefins are given in Tables I and II, respectively. The <M> for the antioxidant would be calculated as follows:

$$\langle M \rangle = (f_{aqueous}+f_{acidic})(M_{10\%\ Ethanol})+f_{alcohol}(M_{50\%\ Ethanol})+f_{fatty}(M_{Miglyol\ 812^{TM}})$$

$$= 0.68(0.060\ mg/kg)+0.01(0.092\ mg/kg)+0.31(7.7\ mg/kg)$$

$$= 2.4\ mg/kg$$

The concentration of the antioxidant in the daily diet resulting from the proposed use would be:

$$CF \times \langle M \rangle = 0.35 \times 2.4\ mg/kg$$

$$= 0.84\ mg/kg$$

If there were no other permitted uses, then the EDI would be calculated using the above value:

$$EDI = 3\ kg\ food/person/day \times 0.84\ mg\ antioxidant/kg\ food$$

$$= 2.5\ mg/person/day$$

Example 2

In a subsequent notification, expanded use of the same antioxidant in polycarbonate and polystyrene food contact articles is described. Each polymer would contact food at or below room temperature. Migration levels are given below:

Solvent	Migration to Food (mg/kg)		
	Polycarbonate	Polystyrene	Impact Polystyrene
10% aq. ethanol	0.020	0.020	0.020
50% aq. ethanol	0.025	0.035	0.22
Miglyol 812	0.033	0.15	6.2

The concentration of the antioxidant in the daily diet resulting from each of the proposed uses is calculated below. A CF of 0.04 for impact polystyrene and a CF of 0.06 for all other polystyrenes was used in the calculation.

Polycarbonates

CF x <M> = 0.05[0.98(0.020 mg/kg)+0.01(0.025 mg/kg)+0.01(0.033 mg/kg)]

= 0.001 mg/kg

Polystyrene

CF x <M> = 0.06[0.52(0.020 mg/kg)+0.01(0.035 mg/kg)+0.47(0.15 mg/kg)]

= 0.0049 mg/kg

Impact Polystyrene

CF x <M> = 0.04[0.86(0.020 mg/kg)+0.04(0.22 mg/kg)+0.10(6.2 mg/kg)]

= 0.026 mg/kg

The total concentration of the antioxidant in the daily diet resulting from the additional uses in polycarbonate and polystyrene is approximately 0.032 mg/kg or 0.032 parts per million (ppm).

The contribution to the EDI is:

EDI = 3 kg food/person/day x 0.032 mg antioxidant/kg g food

= 0.096 mg/person/day

The cumulative exposure from the previously regulated use (Example 1, 2.5 mg/person/day) and the additional proposed uses would be 2.6 mg/person/day.

APPENDIX V.

REFERENCES

General References

American Society for Testing and Materials (ASTM), E 1303-95, Standard Practices for Refractive Index Detectors used in Liquid Chromatography

Arthur D. Little, Inc., July **1983**: A Study of Indirect Food Additive Migration. Final Summary Report. 223-77-2360.

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Arthur D. Little, Inc., August **1990**: High Temperature Migration Testing of Indirect Food Additives to Food. Final Report. FDA Contract No. 223-89-2202.

ASTM E 1511-95, Standard Practice for Testing Conductivity Detectors Used in Liquid or Ion Chromatography.

Baner, A., Brandsch, J., Franz, R. and Piringer, O. , **1996**, The Application of a predictive migration model for evaluating the compliance of plastic materials with European food regulations. *Food Additives and Contaminants*, **13 (5)**, 587-601.

Begley, T. H. and Hollifield, H. C., **1991**, Application of a polytetrafluoroethylene single-sided migration cell for measuring migration through microwave susceptor films. *American Chemical Society Symposium Series 473: Food and Packaging Interactions II*, Chapter **5**, 53-66.

Chang, S., **1984**, Migration of low molecular weight components from polymers: 1. Methodology and diffusion of straight-chain octadecane in polyolefins. *Polymer*, **25**, 209-217.

Currie, L. A., **1968**, Limit of qualitative detection and quantitative determination, application to radiochemistry. *Analytical Chemistry*, **40(3)**, 586-593.

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McNeal, T. P. and Hollifield, H. C., **1993**, Determination of volatile chemicals released from microwave-heat-susceptor food packaging. *J. AOAC International*, **76(6)**, 1268-1275.

National Bureau of Standards, March **1982**: Migration of Low Molecular Weight Additives in Polyolefins and Copolymers. Final Project Report, NBSIR 82-2472. NTIS PB 82-196403, National Technical Information Services, Springfield, VA.

Schwope, A. D. and Reid, R. C., **1988**, Migration to dry foods. *Food Additives and Contaminants*, **5** (Suppl. 1), 445-454.

Schwope, A. D., Till, D. E., Ehntholt, D. J., Sidman, K. R., Whelan, R. H., Schwartz, P. S., and Reid, R. C., **1986**, Migration of an organo-tin stabilizer from polyvinyl chloride film to food and food simulating liquids. *Deutsche Lebensmittel Rundschau*, **82(9)**, 277-282.

Schwope, A. D., Till, D. E., Ehntholt, D. J., Sidman, K. R., Whelan, R. H., Schwartz, P. S., and Reid, R. C., **1987**, Migration of Irganox 1010 from ethylene-vinyl acetate films to foods and food-simulating liquids. *Food and Chemical Toxicology*, **25(4)**, 327-330.

Schwope, A. D., Till, D. E., Ehntholt, D. J., Sidman, K. R., Whelan, R. H., Schwartz, P. S., and Reid, R. C., **1987**, Migration of BHT and Irganox 1010 from low-density polyethylene (LDPE) to foods and food-simulating liquids. *Food and Chemical Toxicology*, **25(4)**, 317-326.

Snyder, R.C. and Breder, C.V., **1985**, New FDA migration cell used to study migration of styrene from polystyrene into various solvents. *Journal of Association Official Analytical Chemist*, **68(4)**, 770-775.

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Till, D. E., Reid, R. C., Schwartz, P. S., Sidman, K. R., Valentine, J. R., and Whelan, R. H., **1982**, Plasticizer migration from polyvinyl chloride film to solvents and foods. *Food and Chemical Toxicology*, **20(1)**, 95-104.

The following are lists of references that contain descriptions, photos, or drawings of migration cells for conducting migration testing for different packaging applications.

<u>Cells for Migration Testing</u>

Conventional Applications

ASTM F34-98, Standard Practice for Construction of Test Cell for Liquid Extraction of Barrier Materials. American Society for Testing and Materials, West Conshohocken, PA 19428-2959

Dow chemical, Inc., A single-sided migration cell, known as the Dow cell, has been used with food oil at 175°C. The cell is available from: Kayeness, Inc., 115 Thousand Oaks Blvd., Suite 101, P.O. Box 709, Morgantown, PA 19543 (610-286-7555). Model no. D9030.

Figge, K. and Koch, J., **1973**, Effect of some variables on the migration of additives from plastics into edible fats. *Food Cosmetics Toxicology*, **11**, 975-988. The cell used was a single-sided cell in contact with food oil at 80°C.

Goydan, R., Schwope, A. D., Reid, R. C., and Cramer, G., **1990**. The cell used was a double-sided (immersion), stainless steel cell, with water, 95% ethanol, and oil at 130°C.

Limm, W. and Hollifield, H., **1995**. The cell used was a single-sided glass cell with water, food oil, and food at 135°C.

Snyder, R.C. and Breder, C.V., **1985**. The cell used was a double-sided (immersion) glass cell with water, 3% acetic acid, 95% ethanol, and oil at 40°C and 50% aqueous ethanol at 70°C. This cell is also specified in ASTM D4754-87 "Standard Test Method for the Two-Sided Liquid Extraction of Plastic Materials Using FDA Migration Cell." American Society for Testing and Materials, West Conshohocken, PA 19428-2959.

Till, D.E., Ehntholt, D. J., Reid, R. C., Schwartz, P. S., Sidman, K. R., Schwope, A. D., and Whelan, R. H., **1982**. The cells used were glass, single-sided and double-sided (immersion) cells, with water, 3% acetic acid, 95% ethanol, and oil at 40°C.

Microwave Applications

ASTM F1349-91, Standard Test Method for Nonvolatile Ultraviolet (UV) Absorbing Extractables from Microwave Susceptors. American Society for Testing and Materials, West Conshohocken, PA 19428-2959.

Begley, T. and Hollifield, H., **1991**. The cell was used with food oil at temperatures up to 240°C.

Rijk, R. and De Kruijf, N., **1993**, Migration testing with olive oil in a microwave oven. *Food Additives and Contaminants*, **10(6)**, 631-645.

Attachment 1
FDA Form No. 3480, "Notification for New Use of a Food Contact Substance"

Form Approved. O.M.B. No.	Approval Expires

U.S. Food and Drug Administration

NOTIFICATION FOR NEW USE OF A FOOD CONTACT SUBSTANCE

FOR NEW USES OF FOOD CONTACT SUBSTANCES

AGENCY USE ONLY

Date of Receipt

When completed send this form and notification to

NOTIFICATION CONTROL ASSISTANT
OFFICE OF PREMARKET APPROVAL
HFS-200
200 C STREET, SW
WASHINGTON, D.C. 20204

Enter the total number of pages in the Premarket Notification		Date Effective (if effective)	PMN Number

GENERAL INSTRUCTIONS

PMN-

- You must provide all information requested in this form to the extent that it is known to or reasonably ascertainable by you. You should make reasonable estimates if you do not have actual data.
- Before you complete this form, you should read the appropriate guidance for completion of notification for food contact substances.

Part I — GENERAL INFORMATION

Only one new use of a food contact substance may be the subject of a particular notification. A "new" use is one not otherwise authorized. If authorization is sought for use of multiple food contact substances, separate notifications should be submitted for each new use. Any accompanying information for a notification may be provided to FDA in a Food Additive Master File and referenced in a notification. Any information referenced in a notification must be submitted to FDA prior to your notification. If you reference information from a third party that is located in other FDA files, Provide a letter of authorization for such use, if necessary. For example, authorization is not necessary to reference publicly available information in FDA's files. If third party authorization is required, provide the name of the authorizing official for the third party and a mailing address.

Completion of this form alone may not constitute a complete notification for a new use of a food contact substance. A notifier must also submit all data and information that forms the basis of the notifier's safety determination for the use that is the subject of the notification and any data and information required by regulation. Five copies of your complete notification must be submitted, each with a completed and signed original or copy of this form.

Part II — CHEMISTRY INFORMATION

Summarize all pertinent information concerning the food contact substance that is the subject of the notification. This should include: chemical identity, manufacturing process, physical properties and specifications, conditions of use, intended technical effect, and stability data. In addition to the summary information provided, your notification should include all supporting information or data. Also, include sufficient data to enable FDA to determine the estimated daily intake resulting from the intended use of the substance. For information on recommendations on migration testing and presentation of the chemistry information see "Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations.

Part III — TOXICITY AND SAFETY INFORMATION

Include summary information on all relevant toxicity studies. In addition to summary information provided here, your notification should include toxicological profiles for each of the relevant studies listed here and should discuss each study in relation to your safety determination. For information on recommendations for types of toxicity testing and the presentation of toxicity data see "Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Toxicology Recommendations".

Part VI — LIST OF ATTACHMENTS

Attach additional sheets if there is not enough space to answer a question fully. Label each continuation sheet with the corresponding section heading. List these attachments, any test data or other data and any optional information included in the notification.

OPTIONAL INFORMATION

You may include any information that you want FDA to consider in evaluating this notification.

CONFIDENTIALITY OF INFORMATION

By submitting a notification under section 409(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(h)), a notifier waives any claim to confidentiality for information necessary to describe the food contact substance and the intended conditions of use that are the subject of the notification. If you are claiming any information in this notification to be confidential you should submit a redacted copy of the notification. FDA may disagree regarding the disclosability of information claimed confidential.

PUBLIC BURDEN STATEMENT

Public reporting burden for this collection of information is estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Premarket Approval (0910-0014), 200 C Street, SW (HFS-200), Washington, DC 20204. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

Part I — GENERAL INFORMATION

1a. Person Submitting Notice

Name of authorized official	Position
[redacted]	[redacted]

Company

[redacted]

Mailing address (number and street)

[redacted]

City, State, ZIP Code, Country

[redacted]

Telephone No.	Fax No.	E-Mail Address
[redacted]	[redacted]	[redacted]

☐ Please check here if E-Mail is your preferred method of communication.

b. Agent (if applicable)

Name of authorized official	Position
[redacted]	[redacted]

Company

Mailing address (number and street)

City, State, ZIP Code, Country

[redacted]

Telephone No.	Fax No.	E-Mail Address
[redacted]	[redacted]	[redacted]

☐ Please check here if E-Mail is your preferred method of communication.

2. If you had a prenotification communication (PNC) concerning this notification and FDA assigned a PNC Number to the communication, enter the number. →	[redacted]	Mark (X) if none → ☐
3. If you previously submitted a PMN for this substance that is not effective, enter the PMN number assigned by FDA. →	[redacted]	Mark (X) if none → ☐
4. List all effective notifications for the substance. → FDA maintains a list of effective notifications accessible through its internet site at "www.FDA/GOV".	[redacted]	Mark (X) if none → ☐

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE

Section A - IDENTIFICATION OF THE FOOD CONTACT SUBSTANCE

1. Chemical Identity

a. Chemical Abstracts Service (CAS) name

[redacted]

b. Other chemical names (IUPAC, etc.)

[redacted]

c. Trade or common names

[redacted]

d. CAS Registry Number

[redacted]

e. Composition

Provide a description of the food contact substance, including chemical formula(e), structures and molecular weight(s). For substances that cannot be represented by a discrete chemical structure, such as polymers, provide a representative chemical structure(s).

For polymers, submit the Mw, Mn, and molecular weight distribution (including method) and, for copolymer, the ratio of monomer units in the copolymer.

[redacted]

☐ Mark (X) this box if you attach a continuation sheet.

f. Characterization

As appropriate, attach data to characterize the substance, including infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), or mass spectra, or other similar data for identification.

☐ Please check here if any of this information is attached and list the items below.

☐ Mark (X) this box if you attach a continuation sheet.

Section A - IDENTIFICATION - Continued

2. Manufacturing Process

a. List below all reagents, monomers, solvents, catalyst systems, purification aids, etc. used to manufacture the food contact substance, their chemical names, CAS Registry Numbers, impurities in each, the typical composition range of each in the total reaction mixture, and the maximum residual of each in the food contact substance intended to be marketed

Chemical Name (1)	CAS Reg. No. (2)	Major Impurities (3)	Typical Composition (4)	Maximum residual (5)
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %

b. Describe the manufacturing process, including times and temperatures, and include chemical equations for all synthetic steps and side reactions. Account for the fate of all substances listed in II.A.2.a.(1) that will not remain as residuals under II.A.2.a.(5). Describe any purification steps.

[redacted]

☐ Mark (X) this box if you attach a continuation sheet.

Section A - IDENTIFICATION - Continued

c. List impurities in the food contact substance including; the chemical name, CAS Registry Number, typical composition (percent weight) in the food contact substance intended for market, and the maximum residual in the food contact substance intended for market; for food contact substances that are polymers include typical and maximum residual monomer concentrations. Some of this data may be duplicated form Section II.A.2.a.

Chemical Name (1)	CAS Reg. No. (4)	Typical Composition (2)	Maximum residual (3)
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %

3. Physical Properties and Specifications

a. Provide physical/chemical specifications for the substance (e.g., maximum impurity levels, melting point) and relevant physical properties (e.g., solubility in food stimulants). Complete, to the extent possible, the "Physical and Chemical Properties Worksheet" included as an attachment to this form.

Properties	Values

[redacted]

☐ Mark (X) this box if you attach a continuation sheet.

b. For polymers, provide relevant information on density range, melt flow indexes, glass transition points, morphology, etc. Provide specification test results for at least three production batches of the substances. Attach methods for establishing compliance with specifications. Indicate the maximum percentage of low molecular weight species, not including residual monomers, reactants or solvents, below 500 daltons and 1000 daltons.

Polymer Properties	Values

☐ Mark (X) this box if you attach a continuation sheet.

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE — Continued

Section B - INTENDED USE

1. Describe the intended use of the food contact substance, including maximum use levels (or thickness) in food-contact materials, and types of food-contact articles in which it is expected to be used (e.g., films, coatings, molded articles). State whether single or repeated use is intended. Provide maximum temperatures and times of food contact, referring to classifications in 21 CFR 176.170(c) Table 2 when possible.

[redacted]

☐ Please check here if you attach a continuation sheet.

2. List types of food expected to contact the substance, with examples if known. Refer to classifications in 21 CFR 176.170(c) Table 1 when possible.

[redacted]

☐ Please check here if you attach a continuation sheet.

3. State the intended technical effect of the food contact substance and summarize data establishing the minimum amount of the substance required to achieve the intended technical effect. Attach data demonstrating that the food contact substance will achieve the intended technical effect.

[redacted]

☐ Please check here if you attach a continuation sheet.

Section C - STABILITY DATA

1. Will the FCS degrade, decompose, or undergo any other chemical change under the intended conditions of use? ☐ Yes ☐ No

2. Provide the basis for your conclusion. Attach any supporting data.

[redacted]

☐ Please check here if you attach a continuation sheet.

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE — Continued

Section C - STABILITY DATA - Continued

3. If the answer to C.1. above is "yes", list the degradation products for the FCS, and provide structures, CAS Reg. Nos. and molecular weights below.

[redacted]

☐ Please check here if you attach a continuation sheet.

Section D - ESTIMATED DAILY INTAKE (EDI)

1. Migration Testing and/or Calculations

Note: Summary information on migration testing and/or calculations should be provided here. A full report of all analytical testing, including detailed descriptions of methodology, raw data, and sample instrumental output (spectra, chromatograms, etc.) must be attached. In lieu of conducting migration testing, worst-case migration may be calculated by assuming 100% migration to food, or migration to food may be estimated through the use of different considerations. In such case, provide full details of calculations.

a. Describe test specimen(s), including full composition (e.g., comonomer composition of base polymer, identities and concentrations of adjuvants), dimensions (thickness and surface area), relevant base polymer properties (e.g., density, T_g, T_m, % crystallinity). For polymers, provide levels of residual monomer(s) in the test specimen(s). Indicate whether specimens were extracted by immersion or exposed on a single side.

b. Identify food simulants employed, and times and temperatures of extraction.

c. Summarize results of migration testing. Give average migration values (mg/in²) for all analytes in each solvent at all time points. Provide sample calculations relating the instrumental output to values in mg/in2. For polymers, provide a measure to polymerization and, if possible, characterize the individual low-molecular oligomer components. Also, provide a measure of monomer(s) migration.

d. Provide a summary of method validation results. Give average percent recovery for all analytes, food simulants, and spiking levels. Full details, including description of spiking procedure and calculations, must be included in attached report.

2. Estimated Daily Intake (EDI)

The incremental and cumulative EDI must be calculated by the notifier.

a. Calculate weighted-average migration (<M>) for each migrant by multiplying values measured in food simulants by appropriate food-type distribution (f_T) factors.

b. Calculate concentration of substance(s) in the diet by multiplying <M> value(s) by appropriate consumption factors (CF). Note: If CF values other than those assigned by FDA are used, information supporting derivation and use of such factors must be attached.

c. Calculate EDI, in milligrams per person per day, by multiplying concentration in the diet (expressed as mg per kg, or parts per million) by 3 kilograms/day average diet. Add the calculated EDI to the existing EDI for food-contact substance, if applicable, to determine the cumulative EDI.

Part III — TOXICITY AND SAFETY INFORMATION

Section A - TOXICOLOGY DATA

1. Attach full reports of all toxicity investigations relevant to safety of the food-contact substance. For polymers, include studies conducted on the polymer itself, oligomers, monomers, etc. Copies of articles containing relevant data in the open scientific literature should be provided. Relevant studies include all oral toxicity and genotoxicity studies as well as toxicity studies by non-oral routes, if considered applicable to oral exposure. List all studies including species tested, duration of dosing, and purpose of study (e.g., to assess acute toxicity, mutagenicity, etc.)

TYPE OF STUDY	SPECIES TESTED	SUBSTANCE TESTED	RESULTS (Include NOAEL or LEL)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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Section B - NOTIFICATION SAFETY DETERMINATION

1. Discuss any adverse effects in the study used to derive an acceptable daily intake (ADI) and the dosing levels at which the effects occured.

2. Calculate an acceptable daily intake (ADI) by applying a suitable safety factor to the lowest suitable NOEL. If the food contact substance contains a carcinogenic constituent, estimate the risk associated with the expected daily concentration intake for such constituents.

Part IV — ENVIRONMENTAL IMPACT OF FOOD-CONTACT SUBSTANCE (21 CFR part 25)

All PMN submissions must contain either a claim of categorical exclusion under 21 CFR 25.32 or an environmental assessment (EA) under 21 CFR 25.40. FDA's Guidance for Industry, entitled "Preparing a Claim for Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition", contains information to help you determine whether a claim of categorical exclusion (Section A below) or an EA (Section B below) applies. If an EA is required, the guidance document contains suggested formats for the various types of actions.

A - CLAIM OF CATEGORICAL EXCLUSION

1. Cite the specific section of the CFR under which the categorical exclusion is claimed (21 CFR 25.32 (I), (j), (q), or (r) ________________ .

2. Does your proposed food-contact use comply with the categorical exclusion criteria? ☐ Yes ☐ No

3. To the best of your knowledge, are there any extraordinary circumstances that would require your submission of an EA? ☐ Yes ☐ No

B - ENVIRONMENTAL ASSESSMENT

If an EA is required, state that an EA has been prepared under 21 CFR 25.40, and is attached.

Part V — CERTIFICATION

The accuracy of the statements you make in this notice should reflect your best prediction of the anticipated facts regarding the chemical substance described herein. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

The notifying party certifies that the information provided herein is accurate and complete to the best of his/her knowledge.

[redacted]

Signature of Authorized Official or Agent

Title

Date

PHYSICAL AND CHEMICAL PROPERTIES WORKSHEET

To assist FDA's review of physical and chemical properties data, please complete the following worksheet for data you provide and include it in the notice. Identify the property measured, the page of the notice on which the property appears, the value of the property, and the units in which the property is measured (as necessary). The measured properties should be for the food contact substance as proposed for use. Properties that are measured for mixtures or formulations should be so noted (%PMN substance in ___). You are not required to submit this worksheet; however, FDA strongly recommends that you complete the worksheet and submit it as a supplement to your test data. This worksheet is not a substitute for submission of test data.

Property (a)	Mark (X) if provided	Page number (b)	Value ©	Measured or Estimate (M or E)
Physical state of the substance	☐		☐ (s) ☐ (l) ☐ (g)	
Vapor pressure @ Temperature ___ °C	☐		Torr	
Density/relative density (specify temperature)	☐		g/cm3	
Solubility @ Temperature ___ °C Solvent ___	☐		g/L	
Solubility in water @ Temperature ___ °C	☐		g/L	
Melting Temperature	☐		°C	
Boiling/sublimation temperature @ ___ torr pressure	☐		°C	
Spectra	☐			
Dissociation constant	☐			
Particle size distribution	☐			
Octanol/water partition coefficient	☐			
Henry's Law constant	☐			
pH ___ @ concentration ___	☐			
Adsorption/coefficient	☐			
Other - Specify ___	☐			
Polymer specific (If a range is applicable, indicate so) % crystallinity of polymer	☐			
Degree of orientation	☐			
Thermal transitions of polymer (i.e., Tg, Tm)	☐			
Density of polymer (specify temperature)	☐			
	☐			

Part VI — LIST OF ATTACHMENTS

Attach continuation sheets for sections of the form and test data and other data (including physical/chemical properties and structure/activity information), and optional information after this page. Clearly identify the attachment and the section of the form to which it relates, as appropriate. Number consecutively the pages of the attachments. In the column below, enter the inclusive page numbers of each attachment. Notifiers need not list other components of their notification not specifically referenced in this form.

Attachment name	Attachment page number(s)
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☐ Mark (X) this box if you attach a continuation sheet. Enter the attachment name and number.

Guidance for Industry

Preparation of Premarket Notifications for Food Contact Substances: Toxicology Recommendations

Additional copies are available from:
Office of Premarket Approval (OPA), HFS-215
Center for Food Safety & Applied Nutrition (CFSAN)
Food and Drug Administration (FDA)
200 C. St., SW.
Washington, DC 20204

(Tel) 202-418-3100

U. S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition (CFSAN)
September, 1999

HIGHLIGHTS OF THE 1999 "GUIDANCE FOR INDUSTRY PREPARATION OF PREMARKET NOTIFICATIONS FOR FOOD CONTACT SUBSTANCES: TOXICOLOGY RECOMMENDATIONS."

- **Safety Narrative (SN) and Comprehensive Toxicological Profile (CTP).** The toxicology data package for a premarket notification should contain both a safety narrative and comprehensive toxicological profile of the food contact substance that is the subject of the notification. The SN should provide the basis for the notifier's determination that the intended use of the food contact substance is safe. The CTP should provide summaries and critical evaluations of all of the available toxicological information pertinent to the safety evaluation of the food contact substance. In some cases, notifications may need to include CTPs for toxicologically relevant constituents of the food contact substance. If a constituent of a food contact substance is carcinogenic, the notification should include a quantitative risk assessment .

- **Toxicity Testing Recommendations for Food Contact Substances and Their Constituents.** This document recommends toxicity testing to assess the potential carcinogenicity and subchronic toxicity of food contact substances that are the subject of premarket notifications and their constituents. The recommendations describe the minimum level of toxicity testing generally considered appropriate at various cumulative estimated daily intakes (CEDIs).[1] At CEDIs of the food contact substance < 0.5 ppb, no toxicity tests are recommended.[2] FDA intends to require, under the authority of 21 U.S.C. 348(h)(3)(B), at CEDIs ≥ 1part per million (ppm), that, ordinarily, a food additive petition be submitted for the use of a food contact substance. In some cases, toxicity testing may need to be approached on a case-by-case basis if indicated by the intended use or potential toxicity of a food contact substance.

- **Evaluation of Structural Similarities to Known Toxicants**. To the extent feasible, knowledge in predicting potential toxicity based on structure/activity relationships may be incorporated into the safety assessment of food contact substances that are the subject of premarket notifications. Such information may be used as part of an overall strategy for assessing the safety of a food contact substance or to help interpret toxicity test results.

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1 FDA recognizes that this guidance's use of cumulative estimated daily intake (CEDI) appears to differ from the approach of FDA's threshold of regulation (TOR) process, 21 CFR 170.39. The two approaches are, in fact, consistent. Under TOR, indirect food additive uses that result in incremental exposures of less than 0.5 ppb in the diet are eligible for exemption from the food additive petition requirement. At the time the TOR program was established, FDA determined that, because of the conservative assumptions ordinarily applied in estimating exposure, the cumulative exposure from a limited number of trivial food additive uses is not likely to be more than negligible. Accordingly, in the case of the TOR exposure levels, it was not necessary to utilize cumulative exposure levels. FDA believes that the determination made in TOR is still sound.

2 However, if multiple trivial uses of a food contact substance result in a significant increase in the CEDI, this will be considered by FDA in determining whether additional toxicity testing is necessary.

- **FDA Form No. 3480**. FDA Form No. 3480 "Notification for New Use of a Food Contact Substance" is attached.

TABLE OF CONTENTS

I. **INTRODUCTION** 5

II. **EXPOSURE ESTIMATES** 5

III. **TEST SUBSTANCE** 6

IV. **GENERAL SAFETY ASSESSMENT APPROACH** 6
- A. Safety Narrative 7
- B. Comprehensive Toxicological Profile(s) (CTPs) 7
- C. Minimum Toxicity Testing Recommendations 9
  1. Cumulative dietary concentrations ≤0.5 ppb 9
  2. Cumulative dietary concentrations >0.5 and ≤50 ppb 10
  3. Cumulative dietary concentrations >50 and ≤1 ppm 10
  4. Cumulative dietary concentrations >1 ppm
- D. Risk Assessment for Carcinogenic Constituents of Food Contact Substances 11
- E. Evaluation of Structural Similarity to Known Toxicants 12
- F. Pre-submission Meetings 12

V. **TOXICOLOGY TESTING PROTOCOLS** 13

VI. **RECOMMENDED ORGANIZATION, FORMAT, AND SIGNIFICANCE OF ELEMENTS OF THE TOXICOLOGY DATA PACKAGE** 14

VII. **POINTS TO CONSIDER IN DETERMINING THE SUITABILITY OF SUBMITTING A PREMARKET NOTIFICATION FOR A FOOD CONTACT SUBSTANCE** 18

VIII. **REFERENCES** 22

I. INTRODUCTION

Section 309 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), amended Section 409 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. 348) to establish a premarket notification (PMN) procedure as the primary method by which the Food and Drug Administration (FDA) regulates food additives that are food contact substances. Food contact substances include all substances that are intended for use as components of materials used in manufacturing, packing, packaging, transporting, or holding food if the use is not intended to have any technical effect in the food.

Notifications for food contact substances must contain sufficient scientific information to demonstrate that the substance that is the subject of the notification is safe for the intended use (21 U.S.C 348(h)(1)). Because the safety standard is the same for all food additives whether subject to the petition process or the PMN process, information in a PMN should be comparable to that required in a food additive petition.

This guidance has been prepared by the Office of Premarket Approval of the Center for Food Safety and Applied Nutrition (CFSAN) at the Food and Drug Administration in accordance with FDA's "Good Guidance Practices" (62 FR 8961; Feb. 27 1997). The purpose of this document is to provide general guidance for the toxicology information that should be included in a PMN for an FCS. The guidance represents FDA's current thinking on the toxicology information for a PMN. It does not create or confer any rights for or on any person and does not operate to bind the Agency or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations. For situations not addressed in this guidance, notifiers are advised to consult FDA. Periodically, FDA will update his guidance in light of new information.

II. EXPOSURE ESTIMATES

The level of toxicology testing that is recommended to support a premarket notification for a food contact substance is largely determined by the CEDI of (alternatively, "the exposure to") the food contact substance. The CEDI is the sum of the EDIs to the food contact substance that may result from the application of the substance described in the notification and any other food uses of the substance. For information on estimating human dietary exposures, refer to the document entitled *Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations* (1999).

In some cases, limitations in the submitted chemistry information could affect the magnitude of the exposure estimate, and thereby affect the toxicological testing recommendations. Therefore, FDA recommends that notifiers provide adequate information on the level of the food contact substance expected in foods in order for an estimate of the CEDI to reflect probable consumer exposure to the food contact substance and to ensure that the appropriate level of toxicity testing is conducted.

III. TEST SUBSTANCE

The Agency generally recommends that the test substance for toxicity studies be identical to the substance that is expected to migrate to food. Ordinarily, the appropriate test substance is the food contact substance itself. In some cases, however, appropriate test substances may include various constituents of the food contact substance, such as minor components, materials used in manufacturing, or decomposition products, if these constituents are expected to migrate to food. For example, for a food contact substance that is a polymer, low-molecular weight oligomers (but not the polymer itself) may be expected to migrate to food from the food contact substance. In this case, FDA recommends that low-molecular weight oligomers be used as the test substances for toxicity studies.

Some food contact substances decompose to other substances that exert technical effects during the manufacture of the food contact substance (e.g., slimicides) or in the food contact substance itself (e.g., phosphorus-based antioxidants in which phosphorus oxidizes to phosphates and phosphites). Other food contact substances, such as antioxidants in polymers, are known to decompose during processing, in storage, and in food or food-simulating solvents. In such cases, decomposition products of the food contact substances may be appropriate test substances for toxicity studies.

Test and control substances should be characterized and handled in accordance with the Good Laboratory Practice regulations for non-clinical laboratory studies (21 CFR Part 58, Subpart F Test and Control Articles). In all cases, the composition of the test substance used in toxicity studies should be known. Notifiers should provide the names, structural formulae, and quantities of major components and other constituents of the test substance, and the approximate total quantity of unidentified material. Common names and trade names should be provided, if available. A single batch of a test substance should be used for a toxicity study, if possible. If more than one batch is used, however, the strength, composition, purity, and other characteristics of each batch should be approximately the same.

Additional information is contained in the document *Draft Guidance for Industry: Preparation of the Chemistry Section of Premarket Notifications Submitted for Food Contact Substances* (1999). For guidance on toxicity studies for specific test substances, notifiers are advised to contact the Agency.

IV. GENERAL SAFETY ASSESSMENT APPROACH

The information provided in this document is intended to help ensure that sufficient toxicology information is available on a food contact substance and its constituent(s) (e.g., manufacturing materials and decomposition products) to determine whether the substance is safe under its intended conditions of use. Although the information contained in this document represents the Agency's current thinking on the toxicology information needed to establish the safety of food contact substances and their constituents, an alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

Information on the appropriate format and organization of toxicology information in the toxicology data package is provided (see VI).

A. Safety Narrative

Each notification should contain a concise safety narrative (SN). The SN should summarize the information that the notifier believes justifies a conclusion that the intended use of a food contact substance is safe. Ordinarily, the SN should reference the estimated human exposure and potential toxicity of the food contact substance and its constituent(s) (e.g. manufacturing materials and decomposition products), and should be based on chemistry and toxicology information and analyses described in detail in other sections of the notification. The SN should include conclusions regarding the mutagenic and carcinogenic potential of the food contact substance, and any toxicologically relevant constituents, as appropriate. In the SN, the notifier should be explicit in reporting all effects of a food contact substance, including those considered adverse or physiologic. If an Acceptable Daily Intake (ADI) for the food contact substance is determined, it should be justified in terms of the end-point chosen, the animal species selected, and the safety (or uncertainty) factor applied. Generally, an ADI for a food contact substance with an exposure below 50ppb is not available because chronic or subchronic studies are not usually recommended for exposures below 50ppb. In cases where such studies are available, an ADI may be calculated. If a previously established ADI is believed to justify the new intended use of a food contact substance, this justification should be discussed.

B. Comprehensive Toxicological Profile (CTP)

Each notification should include a comprehensive toxicological profile (CTP) for the food contact substance that is the subject of the notification. If there are constituent(s) of the food contact substance (e.g., manufacturing materials and decomposition products) that are expected to migrate to food and be present in the human diet, then CTPs for constituents of potential toxicological concern should also be provided in the notification.

CTPs should summarize and evaluate all toxicology studies and related information available on a particular substance. Studies or information recommended below (see IV.C.) that identify adverse effects of the substance, or that bear significantly on the determination of an acceptable daily intake (ADI) for the substance, should be described in detail (see VI.).

Toxicological data obtained via the oral route are considered most relevant to the safety assessment of substances in food. The data collected from studies using other routes of administration may be of value when systemic effects at distal sites are observed. Generally, information and data related to local effects in animals or humans, such as skin and eye irritation, are of limited value in assessing the safety of food contact substances. Studies and information that are determined to be of limited value should be described briefly.

CTPs should contain a no-observed-effect level (NOEL) for each non-neoplastic adverse effect of the substance; NOELs should be based on the study, species, strain and sex that appear to be most sensitive to an identified adverse effect, unless there is a scientific rationale that justifies an alternative approach. The NOEL for each identified adverse effect should be multiplied by the appropriate safety factor. FDA recommends that the lowest value calculated among the set of identified adverse effects be considered the acceptable daily intake (ADI), unless there is scientific rationale that justifies an alternative approach for determining acceptable intake. In general, FDA recommends that a safety factor of 1/1000 should be used for NOELs derived from subchronic studies (i.e., 90-days to one year in duration) and a safety factor of 1/100 should be used for NOELs derived from chronic studies (i.e., one year or longer in duration). For reproduction and developmental endpoints, FDA recommends that a safety factor of 1/1000 should be used if the observed effects are severe or irreversible (e.g., a missing limb or decrease in the number of pups born live); otherwise, FDA recommends a safety factor of 1/100 be used.

The NOELs used to calculate ADIs should be expressed as mg per kg body weight of the test animal. If the levels of the food contact substance or constituents given to test animals in a study are expressed as percent or parts per million in the diet, the notifier should report the NOEL using these units and also calculate intake as mg per kg body weight. The notifier should clearly indicate if actual food consumption data were used in such calculations.

FDA believes that information on the genetic toxicity and carcinogenicity of a substance is important to the safety assessment of such substance, even when the substance is expected to be present in the diet only at a very low level. Thus, information on the genetic toxicity and potential carcinogenicity of the food contact substance and its constituents should be described in detail in the CTPs. Factors to consider in determining whether results of genetic toxicity studies indicate a potential carcinogenic concern for the substance include 1) other available safety data; 2) the array of positive and negative genetic toxicity test results; 3) the estimated cumulative dietary concentration of the substance; and, 4) the chemical structure of the substance (see IV.E.).

In preparing a toxicological profile, the available information should be well organized. For example, the toxicological studies should be grouped according to the duration of exposure (i.e., acute, subacute, subchronic, and chronic). Studies in genetic toxicity, reproduction/teratology, and other specialized areas including pharmacokinetic, immunological, neurotoxicological, clinical, and epidemiological studies, if any, should be grouped separately. When appropriate, data should be presented in tabular form to facilitate their appraisal (e.g., to summarize the results of multiple short-term studies with related endpoints). A list of references should be part of the toxicological profile. Additional recommendations on the format and organization of the CTP are provided below (see VI.A.).

C. Minimum Toxicity Testing Recommendations

The Agency recommends toxicology studies to assess the safety of a food contact substance, and its constituents if appropriate, on the basis of CEDIs. In general, if the EDI for a new use represents a small fraction of the CEDI, and the CEDI is less than an applicable ADI, the notifier may not need to submit any new toxicity data. These recommendations are consistent with the general principle that the potential risk of a substance is likely to increase as exposure increases.

For a food contact substance with a CEDI greater than 0.5ppb, FDA recommends that genetic toxicity testing be done. This is because carcinogenicity is a health concern at low levels of exposure and genetic toxicity testing is the most reliable experimental indicator of potential carcinogenicity, with the exception of full-scale chronic animal carcinogenicity studies. The genetic toxicity tests that are recommended are derived from the report of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In the judgement of the Agency, these tests are generally appropriate for the evaluation of food contact substances. In some cases, genetic toxicity testing may not be useful or the recommendations that are provided below may need to be modified. For example, the Agency believes that genetic toxicity testing of polymers is unnecessary and that testing of oligomers and other constituents that can migrate into foods is more appropriate. Another example is the case of a biocidal substance where a microbial assay would be inappropriate.

This guidance permits notifiers to exercise their own judgement in selecting toxicity tests, including genetic toxicity tests, to be performed for food contact substances. The level of testing and types of toxicology information needed for determining the safety of a particular food contact substance or its constituent(s) should be evaluated on a case-by-case basis, with reference to the intended use (i.e., biocides), potential acute and chronic toxicity (eg., signs/symptoms of neurotoxicity and hyperplasia, respectively), and structural alerts.

The Agency recommends that the following toxicology studies be performed to assess the safety of a food contact substance (and its constituents if appropriate) with the indicated cumulative dietary concentrations:

1. CEDIs ≤0.5 ppb

   a. No toxicity studies are recommended for a food contact substance or constituent with a CEDI less than 0.5 ppb.

   b. However, available information on the potential carcinogenicity of such a substance should be discussed in a CTP (e.g., carcinogenicity studies, genetic toxicity studies, structural similarity to known mutagens or carcinogens [see VI.E.]). For a carcinogenic constituent of a food contact substance, the CTP should contain an estimate of the potential human risk from the constituent due to the proposed use of the food contact substance (see IV.D, below).

2. CEDIs >0.5 ppb and ≤50 ppb

a. The potential carcinogenicity of a food contact substance and their constituents should be evaluated using <u>genetic toxicity tests</u>. The recommended genetic toxicity tests include: (1) a test for gene mutations in bacteria and (2) an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells *or* an *in vitro* mouse lymphoma $tk^{+/-}$ assay. The Agency prefers the mouse lymphoma $tk^{+/-}$ assay because this assay measures heritable genetic damage in living cells and is capable of detecting chemicals that induce either gene mutations or chromosomal aberrations, including genetic events associated with carcinogenesis. In performing the mouse lymphoma $tk^{+/-}$ assay, either the soft agar or the microwell method should be used.

b. Other available <u>information on the potential carcinogenicity</u> of these substances should be discussed in CTPs (e.g. carcinogenicity studies, genetic toxicity studies, structural similarity to known mutagens and carcinogens [see VI.E below]). For a carcinogenic constituent of a food contact substance, the CTP should estimate the potential human risk from the constituent due to the proposed use of the food contact substance (see IV.D.).

3. CEDIs >50 and ≤1 ppm

a. The potential carcinogenicity of food contact substances and/or their constituents with CEDIs greater than or equal to 50 ppb but less than 1 ppm should be evaluated using <u>genetic toxicity tests</u>. The recommended genetic toxicity tests include: (1) a test for gene mutations in bacteria; (2) an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells *or* an *in vitro* mouse lymphoma $tk^{+/-}$ assay (the mouse lymphoma assay is preferred); and, (3) an *in vivo* test for chromosomal damage using rodent hematopoietic cells. The Agency prefers the mouse lymphoma $tk^{+/-}$ assay because this assay measures heritable genetic damage in living cells and is capable of detecting chemicals that induce either gene mutations or chromosomal aberrations, including genetic events associated with carcinogenesis. In performing the mouse lymphoma $tk^{+/-}$ assay, either the soft agar or the microwell method should be used.

b. Other available information on the potential carcinogenicity of these substances should be discussed in CTPs (e.g. carcinogenicity studies, genetic toxicity studies, structural similarity to known mutagens or carcinogens [see I.E.]). For a carcinogenic constituent of a food contact substance, the CTP should estimate the potential human risk from the constituent due to the proposed use of the food contact substance (see IV.D).

c. The potential toxicity of a food contact substance and its constituents should be evaluated by two subchronic oral toxicity tests, one in a rodent species and one in a non-rodent species. The studies should provide an adequate basis for determining an ADI for the food contact substance or its constituents in the indicated range of CEDIs. In addition, the results of these studies will help determine whether longer-term or specialized toxicity tests (e.g. metabolism studies, teratogenicity studies, reproductive toxicity studies, neurotoxicity studies, immunotoxicity studies) are needed to assess the safety of these substances.

4. CEDIs >1 ppm

When the CEDI of a food contact substance or a constituent is expected to be greater than 1 ppm, the Agency expects to require that a food additive petition be submitted for the food contact substance. (see VII.).

D. Risk Assessment for Carcinogenic Constituents of Food Contact Substances

The so-called Delaney clause of the Act's food additive provisions (sec. 409(c)(3)(A)) prohibits the approval of carcinogenic food additives including food contact substances. Importantly, however, the Delaney clause applies to the additive itself and not to constituent chemicals in the additive. Therefore, if a food additive, including a food contact substance, has not been shown to cause cancer but contains an unintended carcinogenic constituent, FDA evaluates the constituent under the general safety standard using quantitative risk assessment procedures. Notifiers should include risk assessments for such constituents, as appropriate, in their notifications. If the calculated upper bound, lifetime risk of a constituent is less than 10^{-8}, the risk associated with the constituent will generally be considered insignificant.

If the results of epidemiology studies or rodent carcinogenicity studies on the constituent are either positive or equivocal, the notifier ordinarily should calculate an extreme-case, upper-bound, lifetime risk to humans from exposure to the constituent. In the absence of convincing scientific evidence that justifies other approaches to estimating risk, the notifier should 1) use the tumor data from the most sensitive species, strain, sex, and study; 2) assume that tumors arising at multiple sites are independent of each other and add their risks; and 3) calculate the extreme-case, upper-bound, lifetime risk by multiplying the unit cancer risk by the estimated human exposure to the constituent based on the use that is the subject of the notification. The unit cancer risk is defined as the slope of a straight line drawn from the lowest apparent effect dose to zero. Unit risks for some constituents of food contact substances have been calculated by the Agency; these are available upon request.

General information on the Agency's approach to risk assessment is contained in publications by Kokoski *et al.* (1990) and Lorentzen (1984). For more specific information on the Center for Food Safety and Applied Nutrition's quantitative risk assessment procedures, notifiers should contact the Agency.

E. Evaluation of Structural Similarity to Known Toxicants

It is reasonable to expect that the chemical structure and physicochemical properties of a food contact substance are potential determinants of toxicity. To the extent feasible, knowledge in predicting toxicity based on structure/activity relationships may be incorporated into the safety assessment of food contact substances. When appropriate, expert analysis, decision-tree procedures (Cramer *et al.*, 1978), or computer-assisted quantitative structure/activity techniques may be used to relate the chemical structure of a food contact substance with a toxicological endpoint of interest. Such information should not be considered as a substitute for actual data, but may be useful in developing an overall strategy for assessing the safety of a food contact substance and interpreting the results of carcinogenicity and other types of toxicology studies.

F. Pre-submission Meetings

A notifier may request a pre-submission meeting regarding a notification for a food contact substance. Many notifications will not require pre-submission interactions (i.e., a routine pre-submission period) between the Agency and the notifier. Such interactions will occur at the discretion of the notifier and are intended to facilitate the submission of successful notifications since notifications without adequate scientific support will be rejected. The Agency considers all pre-submission meetings consultative in nature; such meetings should not be considered determinative with respect to an Agency decision to accept or object to a notification submitted to the Agency subsequent to a pre-submission meeting.

One example of when a pre-submission meeting might be helpful is when the ADI/CEDI ratio is less than five. In such cases, the notifier may wish to request a pre-submission meeting to discuss possible interpretive differences in establishing a NOEL to calculate an ADI. Because dosing levels in toxicology studies are often spaced by a factor of three and the determination of the NOEL would seldom be expected to differ by more than a single dose, FDA believes that this factor of five is an appropriate rule-of-thumb for notifier's to use in determining if a pre-submission meeting is warranted.

Pre-submission meetings may also be helpful when there are questions regarding the carcinogenicity of a food contact substance, significant risk potentially associated with a carcinogenic constituent, or when there are equivocal mutagenicity data.

V. TOXICITY TESTING PROTOCOLS

FDA's Redbook (Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food, 1982) provides general guidance on the conduct of standard toxicity tests, other than genetic toxicology tests, and is relevant to toxicity testing of food contact substances and their constituents. Additional information may also be found in the 1993 draft of Redbook II.

For guidelines on the conduct of genetic toxicity tests, notifiers should consult the upcoming draft of the Redbook to be available on FDA's website. For guidelines for genetic toxicity tests not yet found at this WebSite, FDA recommends that notifiers consult the testing guidelines published by the Organization for Economic Co-operation and Development (http://www.oecd.org/ehs/test/testlist.htm) or the guidelines of the United States Environmental Protection Agency (http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/) and the genotoxicity guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (http://www.ifpma.org/ich5s.html).

Alternative procedures for conducting toxicity tests may be used. In such cases, the Agency recommends that notifiers consult with scientists at the Agency on proposed deviations from recommended toxicity test protocols before the tests are conducted.

All toxicity tests should be conducted according to the good laboratory practice (GLP) regulations of the Food and Drug Administration, or the GLP guidelines of the United States Environmental Protection Agency or the Organization for Economic Co-operation and Development. A statement that the study has been, or will be, conducted in compliance with the good laboratory practice regulations set forth in 21 CFR Chapter 1, Title 21, Part 58 and a quality assurance statement should be part of each nonclinical study submitted in a notice. If a study was not conducted in compliance with the regulations, a brief statement of the reason for noncompliance should be given. For a toxicology study conducted after 1978 that is noncompliant with the GLP regulations, FDA expects to require that notifiers include a report of a data audit by an independent third party auditor if the study is essential to assessing the safety of the food contact substance.

VI. RECOMMENDED ORGANIZATION, FORMAT, AND SIGNIFICANCE OF ELEMENTS OF THE TOXICOLOGY DATA PACKAGE

This section contains FDA's recommendations on the general organization of information and data contained in the toxicological data package (see A below) and on the preparation of study summaries (see B below). Some discussion of how the data obtained from various types of toxicological studies affect the overall safety assessment of a food contact substance is also provided.

A. General Organization

The toxicology data package should be organized as follows:

Part I. Safety Narrative
Part II. Comprehensive Toxicology Profile(s)
Part III. Individual summaries of unpublished study reports and published articles
- A. Genetic toxicity studies
- B. Acute toxicity studies
- C. Short-term toxicity studies
- D. Subchronic toxicity studies
    1. Mouse
    2. Rat
    3. Dog
    4. Other species
- E. Reproductive and developmental studies
- F. Chronic studies
    1. Mouse
    2. Rat
    3. Dog
    4. Other species
- G. Carcinogenicity studies
- H. Special studies

Part 4. Other relevant information
Part 5 Data submission
Part 6. Reference list

Section (B) below discusses study summaries in detail. Information on the Safety Narrative and Comprehensive Toxicological Profile are discussed in sections IV.A and IV.B; data submission and the reference list are discussed in sections VI. C and D.

B. Study Summaries

Individual summaries of unpublished study reports and published articles that bear significantly on the safety assessment of a food contact substance should be prepared and properly referenced. Study reports and published articles of the same study type (i.e., subchronic, chronic, reproductive, etc.) should be grouped first by species (e.g., mouse, rat, dog, etc.), then summarized in chronological order within each grouping. Each summary should include the following minimum information:

- Identity of test substance
- Animal species and strain(s) tested
- Number of animals/sex/dose and control groups
- Route of administration
- Doses (mg/kg bw/day), frequency and duration of dosing, and dosing vehicle(s), if any
- Other elements of study design, as appropriate (recovery phase, culling method, interim kill, etc.)
- Parameters measured (clinical signs, clinical laboratory tests, organ weights, histopathology etc.) and the frequency of measurements
- Significant, compound-related effects (including doses at which effects were observed, incidences of animals with effects, etc.)
- Highest dose(s) at which no substance-related effects were observed (NOEL) expressed in mg/kg bw/day

If the test substance in a specific study differs from the food contact substance that is the subject of the notification, its relationship to the food contact substance should be clearly indicated. For example, the test substance should be identified as a component of the substance, monomer, oligomer, decomposition product, side reaction product, impurity, as appropriate. Other information regarding the test substance is contained in section III above.

A summary table of the effects observed, if any, should be prepared for each study type (i.e., subchronic, chronic, reproductive, etc.) to facilitate the evaluation and determination of no-effect levels for all of the substance-related effects.

C. Significance of Data Types

FDA's views of the relevance of various types of toxicological studies to the safety assessment of a food contact substance are discussed below by study type.

1. Acute Toxicity Studies

Acute toxicity data, including LD_{50} values, are rarely used in the overall safety assessment of food contact substances to which long-term repeated exposure of consumers is expected. It is not necessary to discuss individual acute studies. Instead, the results of acute toxicity studies may be presented in a table.

2. Genetic Toxicity Studies

The potential for genetic toxicity is an important consideration in the safety evaluation of food contact substances with projected levels of dietary exposure above 0.5 ppb. In evaluating the safety of the food contact substance, and related substances if appropriate, notifiers should consider all published and unpublished genetic toxicity data. In summarizing the data, the notifier should:

a. Group the available data by the test system (e.g., gene mutations in bacteria, gene mutations in cultured mammalian cells, chromosome aberrations *in vitro*, chromosome aberrations *in vivo*, etc.). Individual studies within the same test system should be presented in chronological order;

b. Prepare a table of the genetic toxicity data for the food contact substance, and related substances if appropriate; and,

c. Formulate and justify an overall conclusion regarding the genotoxic potential of the food contact substance.

3. Short-term Toxicity Studies

Short-term toxicity studies in animals are usually only 7-28 days in duration. They should not be used to establish an ADI for a food contact substance. Individual summaries of short-term studies should be included in the CTP, but such studies should not be discussed in detail. For these studies, endpoints or target organs potentially associated with toxicity and dose levels appropriate for longer-term toxicity tests should be emphasized, as appropriate.

4. Subchronic Toxicity Studies

NOELs from subchronic toxicity studies often are the basis for determining ADIs for food contact substances. In such cases, it is important to provide complete summaries of subchronic studies, including detailed discussions of the study results. However, if the primary objective of a subchronic study is to identify the target organ or select doses for a longer study, it may be appropriate to limit the discussion as for short-term toxicity studies.

5. Reproductive and Developmental Toxicity Studies

NOELs from reproductive and developmental toxicity studies may be the basis for determining ADIs for food contact substances. Therefore, a summary and detailed discussion of the results of each study should be provided. For both parental animals and their offspring in each generation, no-effect levels should be identified for all substance-related changes. The summaries should state whether the effects used to derive NOELs are considered to be severe or irreversible and discuss the relevance of such severity or reversibility to the selection of the appropriate safety factor for determining an ADI. The toxicological relevance of any reported changes should be evaluated and, if observed, the impact of concurrent maternal toxicity on the results of the study should be addressed.

6. Chronic Toxicity Studies

The results of chronic rodent or non-rodent studies should be summarized and discussed in detail. Due to the increased duration of these studies (i.e., at least a year), toxic effects may be identified that would not be detected in shorter studies. Consequently, if chronic toxicity studies are available, these studies will ordinarily supersede subchronic studies for the purpose of establishing an ADI for a food contact substance, or related substances.

7. Carcinogenicity Studies

All neoplastic and non-neoplastic study observations should be discussed. Summary tables of statistically significant and biologically significant neoplastic and non-neoplastic lesions at any organ/tissue site should be prepared. The incidence of test animals with benign and malignant tumors at a specific organ site, both separately and combined, should be provided as appropriate (McConnell et al., 1986; NTP Guidelines). If available, a detailed morphological description of any significant lesions should be included. Statistical trend tests should be performed in addition to tests of significance between dose and control groups. In addition, all effects observed should be evaluated for potential biological relevance. Related histopathological information, such as time to tumor formation and historical tumor data, should be discussed. Reports prepared by the National Toxicology Program provide good examples of how to present the histopathological data requested above. The CTP should state clearly whether the food contact substance was associated with neoplastic or pre-neoplastic changes and discuss whether the incidence, location and type of tumors observed in this study demonstrate any carcinogenic effects attributable to the food contact substance or related substances, as appropriate. Note that the detailed information described above is particularly needed to support a conclusion that no carcinogenic effects were observed in a study.

8 . Special Studies

This subheading includes metabolism and pharmacokinetic studies, studies designed to test specific toxic effects (e.g. neurotoxicity, immunotoxicity), and observations in humans. Ordinarily, these studies are not a necessary part of the testing paradigm for food contact substances. However, if these studies are available, individual study summaries should be provided. If the results significantly affect the ADI determination for a food contact substance, special studies should be discussed in detail.

D. Data Submission

Full study reports, including the primary data *(i.e.*, individual animal data, plate counts, etc), should ordinarily be submitted for all recommended toxicology studies on the food contact substance, or other substances as appropriate, whether conducted by the notifier or by a third party. It is particularly important that notifiers submit full study reports of studies and related information that are used quantitatively, (e.g., to conduct risk assessments or set no-observed-effect levels). For clarification or to determine if the full study report for a specific toxicology study should be included in a premarket notification, notifiers are advised to contact the Agency after reviewing the information provided in B above. It is not necessary for notifications to include full study reports of all of the data summarized and discussed in the CTP(s) (e.g., occular irritation studies and skin sensitization studies).

E. Reference List

All published and unpublished studies and information presented in the toxicological data package should be appropriately referenced in the text by citing the author(s) publication name, and year of publication. All references should be listed alphabetically. Each published reference should include the names of all authors, the year of publication, the full title of the article, and pages cited. For a reference from a book, also include the title of the book, the editor(s), and the publisher. Reference to unpublished studies should identify all authors, the sponsor of the study, the laboratory conducting the study, the final report date, the full title of the final report, the report identification number, and inclusive page numbers. References to government publications should include the department, bureau or office, title, location of publisher, publisher, year, pages cited, and publication series, and report number or monograph number.

The search parameters that were used for all literature searches conducted should be provided. The parameters of interest including the names of databases searched, the period of years searched, and the specific search terms used.

VII. POINTS TO CONSIDER IN DETERMINING THE SUITABILITY OF SUBMITTING A PREMARKET NOTIFICATION FOR A FOOD CONTACT SUBSTANCE

FDA believes that premarket review and approval of a food additive petition for the use of a food contact substance should be required only in those cases where it is necessary for adequate assurance of safety. FDA expects to propose regulations identifying the circumstances in which a food additive petition would be required for the use of a food contact substance. Such regulations would also permit FDA to accept a notification if the Agency determines that submission and review of a petition are not necessary for adequate assurance of safety.

FDA currently believes that there are two sets of circumstances in which premarket review and approval of a food additive petition for the use of a food contact substance through the petition process are necessary for adequate assurance of safety. These circumstances are:

a) uses of a food contact substance that increase the CEDI of the substance from food uses to greater than 1 part per million (ppm) or, in the case of biocides, to greater than 200 parts per billion (ppb); or

b) when there are one or more carcinogenicity studies on the FCS that have not been previously reviewed by the Agency and which are not clearly negative for carcinogenicity.

These two sets of circumstances are discussed in more detail below.

FDA expects to propose regulations requiring a food additive petition for uses of an FCS that increase the CEDI of the substance from food uses to greater than 1 ppm or, in the case of biocides, to greater than 200 ppb. Historically, FDA has based its recommendations for toxicity data to support the safe use of food additives on the estimated intake of the food additives. As a general rule, higher estimated intakes of substances in the diet pose both an increased risk of toxicity and a wider range of potential toxic effects. The maximum levels of the CEDI identified above are levels at which the agency has historically requested more comprehensive toxicity testing in order to address a substance's potential to induce diverse toxic effects. To address the risk of these effects, FDA has asked for longer term toxicity studies and toxicity studies that measure a wider variety of toxic endpoints. The agency believes that this approach has proved to be sound in that it has ensured the safety of additives permitted in the food supply. Thus, FDA continues to believe that uses of food contact substances that have the potential for inducing diverse toxic effects of consequence to human health generally require longer term and more specialized toxicity testing to support their safe use. Where such toxicity testing is needed, the agency believes that submission, review, and approval of a food additive petition is appropriate because the petition process will afford FDA the time necessary to review the more extensive toxicity data package.

FDA has tentatively concluded that a lower dietary concentration cutoff for PMNs for biocides is appropriate for substances that are toxic by design. Biocides are a class of FCSs that are expected to be more toxic because their intended technical effect is microbial toxicity. Consistent with FDA's testing recommendations, FDA intends that this lower cut-off level would apply to substances used as FCSs primarily for their antimicrobial or fungicidal effects.

The use of carcinogens as food additives is prohibited by the food additives anti-cancer clause in section 409(c)(3)(A) of the act (the so-called Delaney clause). FDA believes that, if data exist that may demonstrate that an FCS is carcinogenic, a thorough review of such data is appropriate and necessary to adequately assure safety and properly administer the statute. The determination of carcinogenic potential is a critical aspect of the safety evaluation that may be too complicated for the Agency to complete within the 120-day time frame allotted for review of food contact substance notifications. Therefore, the Agency expects to propose regulations to require a food additive petition when there are carcinogenicity studies of the FCS that have not previously been reviewed by FDA and that are not clearly negative for carcinogenicity.

FDA's experience in evaluating the safety of food contact substances and their constituents indicates that situations may arise in which a premarket notification will be appropriate for the use of a food contact substance even if the CEDI for the food contact substance or its constituents are equal to or greater than 1 ppm, or 200 ppb in the case of biocides. Examples of such cases are provided below.

Premarket Notification for Food Contact Substances With CEDIs > 1 ppm, or 200 ppb for Biocides

A premarket notification may be appropriate for a food contact substance, even if the CEDI is > 1 ppm, or 200 ppb for biocides, when:

1. There is an existing ADI for the food contact substance and its constituent(s). In such a case, the notifier should contact the Agency to determine the applicability of the ADI for the food contact substance, before submitting a premarket notification.

2. A large database is available on a close structural analog of the food contact substance and its constituent(s), which analog has been approved by the Agency. In such cases, the following toxicological tests are recommended to demonstrate the degree of toxicological and metabolic similarity between the FDA-regulated analog and the food contact substance and its constituent(s): a) a subchronic oral toxicity study in a rodent or non-rodent species and b) comparative absorption, distribution, metabolism, and elimination studies.

3. The food contact substance and/or its constituent(s) is poorly absorbed or is not absorbed from the gastrointestinal tract. Such assertions should be supported by relevant scientific information or data (e.g., the substance is a high molecular weight polymer or is a highly charged substance at gastric pH).

4. The food contact substance undergoes chemical or metabolic transformation solely to products known to be of little toxicological concern at the estimated CEDI. Such assertions should be supported by relevant *in vivo* or *in vitro* data.

VIII. REFERENCES CITED

Cramer, G.M., Ford, R. A., and Hall, R. L. 1978. Estimation of toxic hazard--A decision tree approach. Food Cosmet. Toxicol. 16:255-276.

Code of Federal Regulations, Chapter 1, Title 21, Part 58-Good Laboratory Practice for Non-Clinical Laboratory Studies. Final Rule for Good Laboratory Practice Regulation under the Federal Food, Drug, and Cosmetic Act. Federal Register 43: pp. 59986-60025, Dec. 22, 1978.

Kokoski, C. J., Henry, S. H., Lin, C. S., and Ekelman, K. B. Methods used in safety evaluation. In: Food Additives, edited by Branen, A. L., Davidson, P. M., and Salminen, S., Marcel Dekker, Inc, New York, p. 579-616, 1990.

Lorentzen, R. 1984. FDA Procedures for carcinogenic risk assessment. Food Technology 38(10):108-111.

McConnel E. E., Solleveld, H. A., Swenberg, J. A., and Boorman, G. A. 1986. Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J. Natl. Canc. Inst.* **76**:283-289.

Office of Premarket Approval. 1999. Guidance for Industry Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations, U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, 200 C Street S.W., Washington, D.C. 20204.

FDA. 1982. Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food. The Redbook. U.S. Food and Drug Administration, Bureau of Foods, National Technical Information Service, Springfield, VA.

FDA. 1993. Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food. Draft Redbook II. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Washington, D.C.

Attachment 1
FDA Form No. 3480, "Notification for New Use of a Food Contact Substance"

Form Approved. O.M.B. No. Approval Expires

U.S. Food and Drug Administration

NOTIFICATION FOR NEW USE OF A FOOD CONTACT SUBSTANCE

FOR NEW USES OF FOOD CONTACT SUBSTANCES

AGENCY USE ONLY
Date of Receipt

When completed send this form and notification to	NOTIFICATION CONTROL ASSISTANT OFFICE OF PREMARKET APPROVAL HFS-200 200 C STREET, SW WASHINGTON, D.C. 20204

Enter the total number of pages in the Premarket Notification		Date Effective (if effective)	PMN Number

GENERAL INSTRUCTIONS

PMN-

- You must provide all information requested in this form to the extent that it is known to or reasonably ascertainable by you. You should make reasonable estimates if you do not have actual data.
- Before you complete this form, you should read the appropriate guidance for completion of notification for food contact substances.

Part I — GENERAL INFORMATION

Only one new use of a food contact substance may be the subject of a particular notification. A "new" use is one not otherwise authorized. If authorization is sought for use of multiple food contact substances, separate notifications should be submitted for each new use. Any accompanying information for a notification may be provided to FDA in a Food Additive Master File and referenced in a notification. Any information referenced in a notification must be submitted to FDA prior to your notification. If you reference information from a third party that is located in other FDA files, Provide a letter of authorization for such use, if necessary. For example, authorization is not necessary to reference publicly available information in FDA's files. If third party authorization is required, provide the name of the authorizing official for the third party and a mailing address.

Completion of this form alone may not constitute a complete notification for a new use of a food contact substance. A notifier must also submit all data and information that forms the basis of the notifier's safety determination for the use that is the subject of the notification and any data and information required by regulation. Five copies of your complete notification must be submitted, each with a completed and signed original or copy of this form.

Part II — CHEMISTRY INFORMATION

Summarize all pertinent information concerning the food contact substance that is the subject of the notification. This should include chemical identity, manufacturing process, physical properties and specifications, conditions of use, intended technical effect, and stability data. In addition to the summary information provided, your notification should include all supporting information or data. Also, include sufficient data to enable FDA to determine the estimated daily intake resulting from the intended use of the substance. For information on recommendations on migration testing and presentation of the chemistry information see "Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations.

Part III — TOXICITY AND SAFETY INFORMATION

Include summary information on all relevant toxicity studies. In addition to summary information provided here, your notification should include toxicological profiles for each of the relevant studies listed here and should discuss each study in relation to your safety determination. For information on recommendations for types of toxicity testing and the presentation of toxicity data see "Guidance for Industry: Preparation of Premarket Notifications for Food Contact Substances: Toxicology Recommendations".

Part VI — LIST OF ATTACHMENTS

Attach additional sheets if there is not enough space to answer a question fully. Label each continuation sheet with the corresponding section heading. List these attachments, any test data or other data and any optional information included in the notification.

OPTIONAL INFORMATION

You may include any information that you want FDA to consider in evaluating this notification.

CONFIDENTIALITY OF INFORMATION

By submitting a notification under section 409(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348(h)), a notifier waives any claim to confidentiality for information necessary to describe the food contact substance and the intended conditions of use that are the subject of the notification. If you are claiming any information in this notification to be confidential you should submit a redacted copy of the notification. FDA may disagree regarding the disclosability of information claimed confidential.

PUBLIC BURDEN STATEMENT
Public reporting burden for this collection of information is estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Premarket Approval (0910-0014), 200 C Street, SW (HFS-200), Washington, DC 20204. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

Part I — GENERAL INFORMATION

1a. Person Submitting Notice

Name of authorized official	Position
[redacted]	[redacted]

Company
[redacted]

Mailing address (number and street)
[redacted]

City, State, ZIP Code, Country
[redacted]

Telephone No.	Fax No.	E-Mail Address
[redacted]	[redacted]	[redacted]

☐ Please check here if E-Mail is your preferred method of communication.

b. Agent (if applicable)

Name of authorized official	Position
[redacted]	[redacted]

Company

Mailing address (number and street)
[redacted]

City, State, ZIP Code, Country
[redacted]

Telephone No.	Fax No.	E-Mail Address
[redacted]	[redacted]	[redacted]

☐ Please check here if E-Mail is your preferred method of communication.

2. If you had a prenotification communication (PNC) concerning this notification and FDA assigned a PNC Number to the communication, enter the number. →	[redacted]	Mark (X) if none → ☐
3. If you previously submitted a PMN for this substance that is not effective, enter the PMN number assigned by FDA. →		Mark (X) if none → ☐
4. List all effective notifications for the substance. → FDA maintains a list of effective notifications accessible through its internet site at "www.FDA/GOV".		Mark (X) if none → ☐

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE

Section A - IDENTIFICATION OF THE FOOD CONTACT SUBSTANCE

1. Chemical Identity

a. Chemical Abstracts Service (CAS) name

[redacted]

b. Other chemical names (IUPAC, etc.)

[redacted]

c. Trade or common names

[redacted]

d. CAS Registry Number

[redacted]

e. Composition

Provide a description of the food contact substance, including chemical formula(e), structures and molecular weight(s). For substances that cannot be represented by a discrete chemical structure, such as polymers, provide a representative chemical structure(s).

For polymers, submit the Mw, Mn, and molecular weight distribution (including method) and, for copolymer, the ratio of monomer units in the copolymer.

[redacted]

☐ Mark (X) this box if you attach a continuation sheet.

f. Characterization

As appropriate, attach data to characterize the substance, including infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR), or mass spectra, or other similar data for identification.

☐ Please check here if any of this information is attached and list the items below.

☐ Mark (X) this box if you attach a continuation sheet.

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE — Continued

Section A - IDENTIFICATION - Continued

2. Manufacturing Process

a. List below all reagents, monomers, solvents, catalyst systems, purification aids, etc. used to manufacture the food contact substance, their chemical names, CAS Registry Numbers, impurities in each, the typical composition range of each in the total reaction mixture, and the maximum residual of each in the food contact substance intended to be marketed

Chemical Name (1)	CAS Reg. No. (2)	Major Impurities (3)	Typical Composition (4)	Maximum residual (5)
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %
	[redacted]		[redacted] %	[redacted] %

b. Describe the manufacturing process, including times and temperatures, and include chemical equations for all synthetic steps and side reactions. Account for the fate of all substances listed in II.A.2.a.(1) that will not remain as residuals under II.A.2.a.(5). Describe any purification steps.

[redacted]

☐ Mark (X) this box if you attach a continuation sheet.

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE — Continued

Section A - IDENTIFICATION - Continued

c. List impurities in the food contact substance including; the chemical name, CAS Registry Number, typical composition (percent weight) in the food contact substance intended for market, and the maximum residual in the food contact substance intended for market; for food contact substances that are polymers include typical and maximum residual monomer concentrations. Some of this data may be duplicated form Section II.A.2.a.

Chemical Name (1)	CAS Reg. No. (4)	Typical Composition (2)	Maximum residual (3)
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %
	[redacted]	[redacted] %	[redacted] %

3. Physical Properties and Specifications

a. Provide physical/chemical specifications for the substance (e.g., maximum impurity levels, melting point) and relevant physical properties (e.g., solubility in food stimulants). Complete, to the extent possible, the "Physical and Chemical Properties Worksheet" included as an attachment to this form.

Properties	Values

[redacted]

☐ Mark (X) this box if you attach a continuation sheet.

b. For polymers, provide relevant information on density range, melt flow indexes, glass transition points, morphology, etc. Provide specification test results for at least three production batches of the substances. Attach methods for establishing compliance with specifications. Indicate the maximum percentage of low molecular weight species, not including residual monomers, reactants or solvents, below 500 daltons and 1000 daltons.

Polymer Properties	Values

☐ Mark (X) this box if you attach a continuation sheet.

Part II — INFORMATION ON IDENTITY, USE AND EXPOSURE — Continued

Section B - INTENDED USE

1. Describe the intended use of the food contact substance, including maximum use levels (or thickness) in food-contact materials, and types of food-contact articles in which it is expected to be used (e.g., films, coatings, molded articles). State whether single or repeated use is intended. Provide maximum temperatures and times of food contact, referring to classifications in 21 CFR 176.170(c) Table 2 when possible.

[redacted]

☐ Please check here if you attach a continuation sheet.

2. List types of food expected to contact the substance, with examples if known. Refer to classifications in 21 CFR 176.170(c) Table 1 when possible.

[redacted]

☐ Please check here if you attach a continuation sheet.

3. State the intended technical effect of the food contact substance and summarize data establishing the minimum amount of the substance required to achieve the intended technical effect. Attach data demonstrating that the food contact substance will achieve the intended technical effect.

[redacted]

☐ Please check here if you attach a continuation sheet.

Section C - STABILITY DATA

1. Will the FCS degrade, decompose, or undergo any other chemical change under the intended conditions of use? ☐ Yes ☐ No

2. Provide the basis for your conclusion. Attach any supporting data.

[redacted]

☐ Please check here if you attach a continuation sheet.

Section C - STABILITY DATA - Continued

3. If the answer to C.1. above is "yes", list the degradation products for the FCS, and provide structures, CAS Reg. Nos. and molecular weights below.

[redacted]

☐ Please check here if you attach a continuation sheet.

Section D - ESTIMATED DAILY INTAKE (EDI)

1. Migration Testing and/or Calculations

Note: Summary information on migration testing and/or calculations should be provided here. A full report of all analytical testing, including detailed descriptions of methodology, raw data, and sample instrumental output (spectra, chromatograms, etc.) must be attached. In lieu of conducting migration testing, worst-case migration may be calculated by assuming 100% migration to food, or migration to food may be estimated through the use of different considerations. In such case, provide full details of calculations.

a. Describe test specimen(s), including full composition (e.g., comonomer composition of base polymer, identities and concentrations of adjuvants), dimensions (thickness and surface area), relevant base polymer properties (e.g., density, T_g, T_m, % crystallinity). For polymers, provide levels of residual monomer(s) in the test specimen(s). Indicate whether specimens were extracted by immersion or exposed on a single side.

b. Identify food simulants employed, and times and temperatures of extraction.

c. Summarize results of migration testing. Give average migration values (mg/in²) for all analytes in each solvent at all time points. Provide sample calculations relating the instrumental output to values in mg/in2. For polymers, provide a measure to polymerization and, if possible, characterize the individual low-molecular oligomer components. Also, provide a measure of monomer(s) migration.

d. Provide a summary of method validation results. Give average percent recovery for all analytes, food simulants, and spiking levels. Full details, including description of spiking procedure and calculations, must be included in attached report.

2. Estimated Daily Intake (EDI)

The incremental and cumulative EDI must be calculated by the notifier.

a. Calculate weighted-average migration (<M>) for each migrant by multiplying values measured in food simulants by appropriate food-type distribution (f_T) factors.

b. Calculate concentration of substance(s) in the diet by multiplying <M> value(s) by appropriate consumption factors (CF). Note: If CF values other than those assigned by FDA are used, information supporting derivation and use of such factors must be attached.

c. Calculate EDI, in milligrams per person per day, by multiplying concentration in the diet (expressed as mg per kg, or parts per million) by 3 kilograms/day average diet. Add the calculated EDI to the existing EDI for food-contact substance, if applicable, to determine the cumulative EDI.

Part III — TOXICITY AND SAFETY INFORMATION

Section A - TOXICOLOGY DATA

1. Attach full reports of all toxicity investigations relevant to safety of the food-contact substance. For polymers, include studies conducted on the polymer itself, oligomers, monomers, etc. Copies of articles containing relevant data in the open scientific literature should be provided. Relevant studies include all oral toxicity and genotoxicity studies as well as toxicity studies by non-oral routes, if considered applicable to oral exposure. List all studies including species tested, duration of dosing, and purpose of study (e.g., to assess acute toxicity, mutagenicity, etc.)

TYPE OF STUDY	SPECIES TESTED	SUBSTANCE TESTED	RESULTS (Include NOAEL or LEL)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Section B - NOTIFICATION SAFETY DETERMINATION

1. Discuss any adverse effects in the study used to derive an acceptable daily intake (ADI) and the dosing levels at which the effects occured.

2. Calculate an acceptable daily intake (ADI) by applying a suitable safety factor to the lowest suitable NOEL. If the food contact substance contains a carcinogenic constituent, estimate the risk associated with the expected daily concentration intake for such constituents.

Part IV — ENVIRONMENTAL IMPACT OF FOOD-CONTACT SUBSTANCE (21 CFR part 25)

All PMN submissions must contain either a claim of categorical exclusion under 21 CFR 25.32 or an environmental assessment (EA) under 21 CFR 25.40. FDA's Guidance for Industry, entitled "Preparing a Claim for Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition", contains information to help you determine whether a claim of categorical exclusion (Section A below) or an EA (Section B below) applies. If an EA is required, the guidance document contains suggested formats for the various types of actions.

A - CLAIM OF CATEGORICAL EXCLUSION

1. Cite the specific section of the CFR under which the categorical exclusion is claimed (21 CFR 25.32 (I), (j), (q), or (r) ____________________ .

2. Does your proposed food-contact use comply with the categorical exclusion criteria? ☐ Yes ☐ No

3. To the best of your knowledge, are there any extraordinary circumstances that would require your submission of an EA? ☐ Yes ☐ No

B - ENVIRONMENTAL ASSESSMENT

If an EA is required, state that an EA has been prepared under 21 CFR 25.40, and is attached.

Part V — CERTIFICATION

The accuracy of the statements you make in this notice should reflect your best prediction of the anticipated facts regarding the chemical substance described herein. Any knowing and willful misinterpretation is subject to criminal penalty pursuant to 18 U.S.C. 1001.

The notifying party certifies that the information provided herein is accurate and complete to the best of his/her knowledge.

Signature of Authorized Official or Agent

Title

Date

PHYSICAL AND CHEMICAL PROPERTIES WORKSHEET

To assist FDA's review of physical and chemical properties data, please complete the following worksheet for data you provide and include it in the notice. Identify the property measured, the page of the notice on which the property appears, the value of the property, and the units in which the property is measured (as necessary). The measured properties should be for the food contact substance as proposed for use. Properties that are measured for mixtures or formulations should be so noted (%PMN substance in ___). You are not required to submit this worksheet; however, FDA strongly recommends that you complete the worksheet and submit it as a supplement to your test data. This worksheet is not a substitute for submission of test data.

Property (a)	Mark (X) if provided	Page number (b)	Value ©	Measured or Estimate (M or E)
Physical state of the substance	☐	[redacted]	☐ (s) ☐ (l) ☐ (g)	[redacted]
Vapor pressure @ Temperature [redacted] °C	☐	[redacted]	[redacted] Torr	[redacted]
Density/relative density (specify temperature)	☐	[redacted]	[redacted] g/cm3	[redacted]
Solubility @ Temperature [redacted] °C Solvent [redacted]	☐	[redacted]	[redacted] g/L	[redacted]
Solubility in water @ Temperature [redacted] °C	☐	[redacted]	[redacted] g/L	[redacted]
Melting Temperature	☐	[redacted]	[redacted] °C	[redacted]
Boiling/sublimation temperature @ [redacted] torr pressure	☐	[redacted]	[redacted] °C	[redacted]
Spectra	☐	[redacted]	[redacted]	[redacted]
Dissociation constant	☐	[redacted]	[redacted]	[redacted]
Particle size distribution	☐	[redacted]	[redacted]	[redacted]
Octanol/water partition coefficient	☐	[redacted]	[redacted]	[redacted]
Henry's Law constant	☐	[redacted]	[redacted]	[redacted]
pH [redacted] @ concentration [redacted]	☐	[redacted]	[redacted]	[redacted]
Adsorption/coefficient	☐	[redacted]	[redacted]	[redacted]
Other - Specify [redacted]	☐	[redacted]	[redacted]	[redacted]
Polymer specific (If a range is applicable, indicate so) % crystallinity of polymer	☐	[redacted]	[redacted]	[redacted]
Degree of orientation	☐	[redacted]	[redacted]	[redacted]
Thermal transitions of polymer (i.e., Tg, Tm)	☐	[redacted]	[redacted]	[redacted]
Density of polymer (specify temperature)	☐	[redacted]	[redacted]	[redacted]
[redacted]	☐	[redacted]	[redacted]	[redacted]

Part VI — LIST OF ATTACHMENTS

Attach continuation sheets for sections of the form and test data and other data (including physical/chemical properties and structure/activity information), and optional information after this page. Clearly identify the attachment and the section of the form to which it relates, as appropriate. Number consecutively the pages of the attachments. In the column below, enter the inclusive page numbers of each attachment. Notifiers need not list other components of their notification not specifically referenced in this form.

Attachment name	Attachment page number(s)
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☐ Mark (X) this box if you attach a continuation sheet. Enter the attachment name and number.